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**(54) PROCESSES AND INTERMEDIATES FOR PREPARING A MACROCYCLIC PROTEASE
INHIBITOR OF HCV**

VERFAHREN UND ZWISCHENPRODUKTE ZUR HERSTELLUNG EINES MAKROCYCLISCHEN
INHIBITORS VON HCV-PROTEASE

PROCÉDÉS ET INTERMÉDIAIRES POUR PRÉPARER UN INHIBITEUR MACROCYCLIQUE DE
PROTÉASE DU VHC

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(56) References cited:
WO-A-2005/073195 WO-A-2008/092955

• **ROSENQUIST ASA ET AL: "Synthesis of
enantiomerically pure trans-3,4-substituted
cyclopentanol by enzymatic resolution" ACTA
CHEMICA SCANDINAVICA, MUNKSGAARD,
COPENHAGEN, DK, vol. 46, no. 11, 1 January
1992 (1992-01-01), pages 1127-1129,
XP009099339 ISSN: 0904-213X cited in the
application**

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Description

Field of the invention

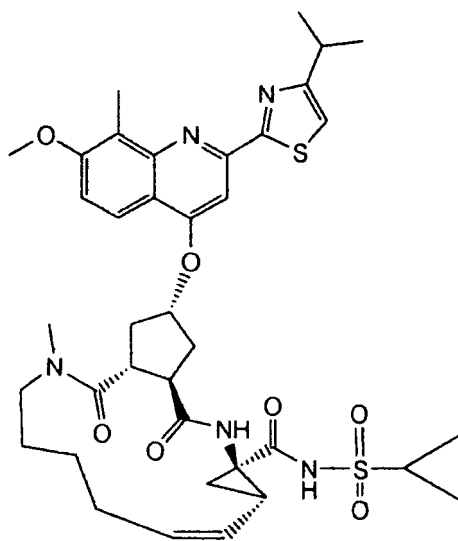
[0001] The present invention relates to synthesis procedures and synthesis intermediates of a macrocyclic protease inhibitor of the hepatitis C virus (HCV).

Background of the Invention

[0002] Hepatitis C virus (HCV) is the leading cause of chronic hepatitis, which can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma), making it the leading cause of liver transplantations. Current anti-HCV therapy, based on (pegylated) interferon-alpha (IFN- α) in combination with ribavirin, suffers from limited efficacy, significant side effects, and is poorly tolerated in many patients. This prompted the search for more effective, convenient and better-tolerated therapy.

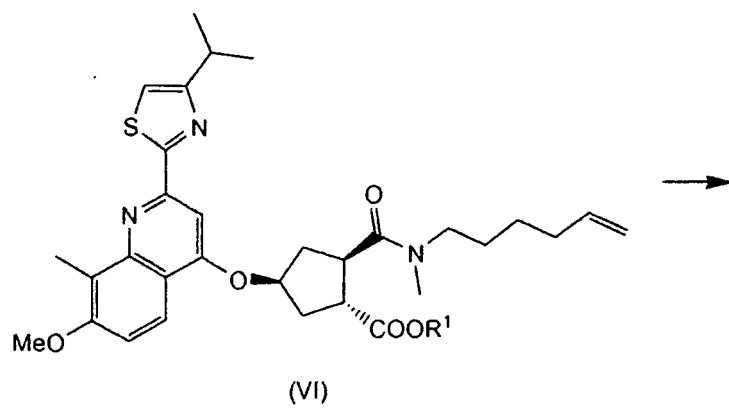
[0003] Replication of the genome of HCV is mediated by a number of enzymes, amongst which is HCV NS3 serine protease and its associated cofactor, NS4A. Various agents that inhibit this enzyme have been described. WO 05/073195 discloses linear and macrocyclic NS3 serine protease inhibitors with a central substituted proline moiety and WO 05/073216 with a central cyclopentyl moiety. Amongst these, the macrocyclic derivatives are attractive by their pronounced activity against HCV and attractive pharmacokinetic profile.

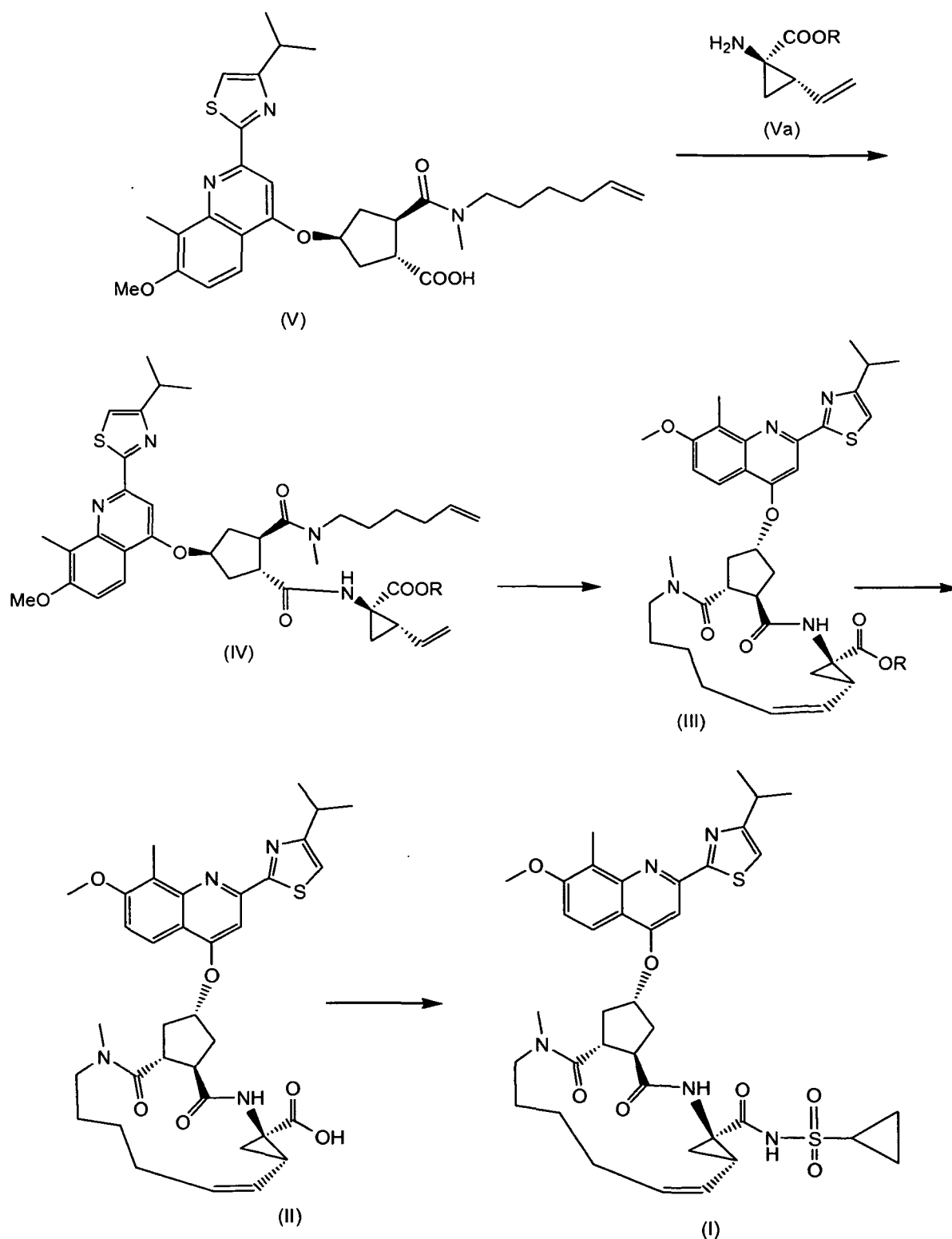
[0004] WO 2007/014926 describes macrocyclic cyclopentyl and proline derivatives including the compound of formula (I), with the structure represented hereafter. The compound of formula (I) is a very effective inhibitor of the HCV serine protease and is particularly attractive due to its favorable pharmacokinetical profile. Because of its properties this compound has been selected as a potential candidate for development as an anti-HCV drug. Consequently there is a need for producing larger quantities of this active ingredient based on processes that provide the product in high yield and with a high degree of purity. WO 2008/092955 describes processes and intermediates to prepare the compound of formula (I).



(I)

[0005] The compound of formula (I) can be prepared starting from an intermediate (VI), wherein the ester function is hydrolysed, yielding carboxylic acid (V), which in turn is coupled in an amide forming reaction with the cyclopropyl amino acid (Va). The resulting intermediate (IV) is cyclized by an olefin metathesis reaction in the presence of a suitable metal catalyst such as e.g. an ylide Ru-based catalyst. The resulting macrocyclic ester (III) is then hydrolyzed to macrocyclic acid (II). The latter is coupled with a sulfonamide (V) in an amide forming reaction to yield the end product (I). These reactions are outlined in the reaction scheme herebelow. In this and the following reaction schemes or representations of individual compounds, R is C₁₋₄alkyl, in particular R is C₁₋₃alkyl, more in particular R is C₁₋₂alkyl, or in one embodiment R is ethyl. R¹ is C₁₋₄alkyl, in particular R¹ is C₁₋₃alkyl, more in particular R¹ is C₁₋₂alkyl, or R¹ is methyl; or R¹ is ethyl.



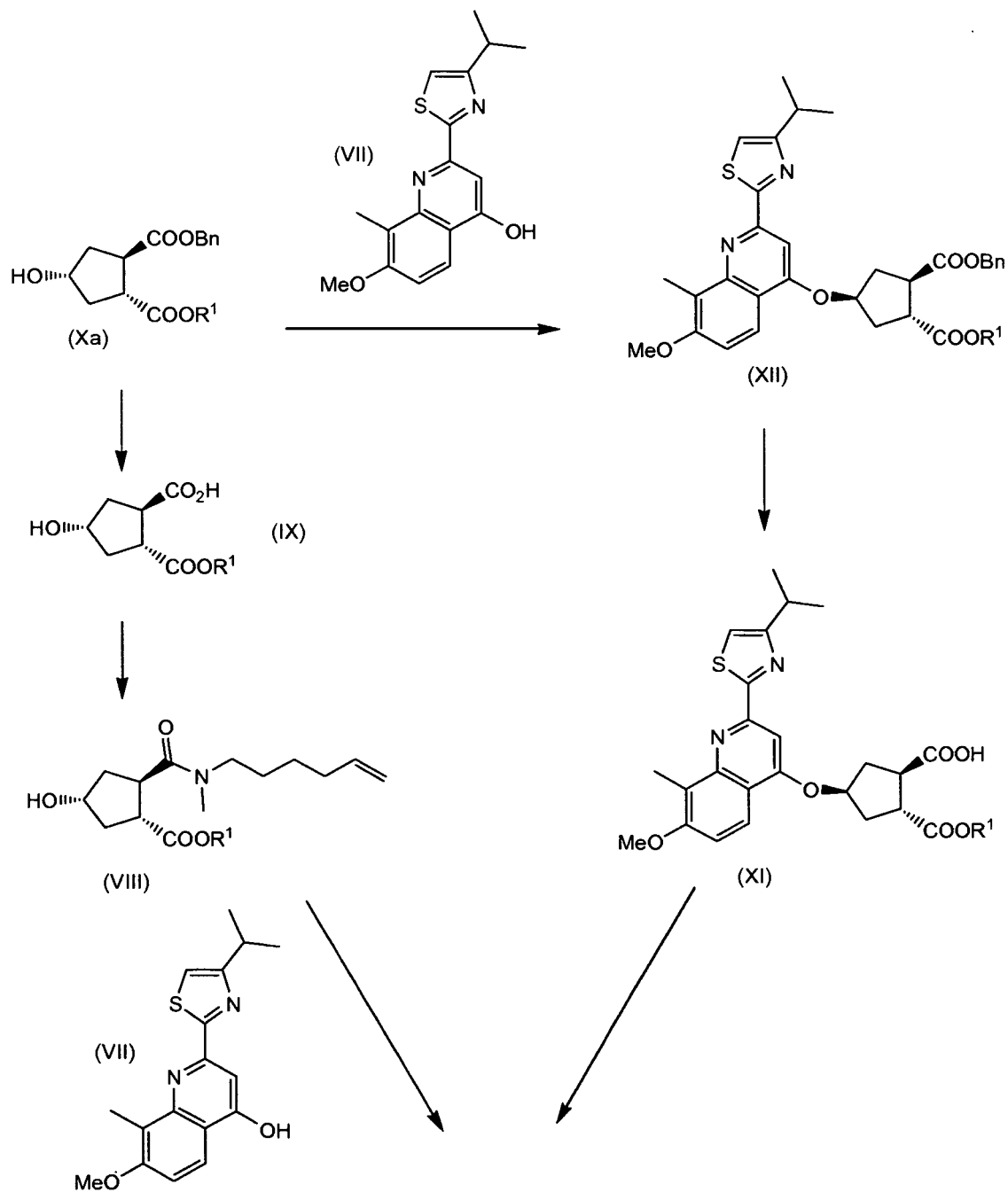


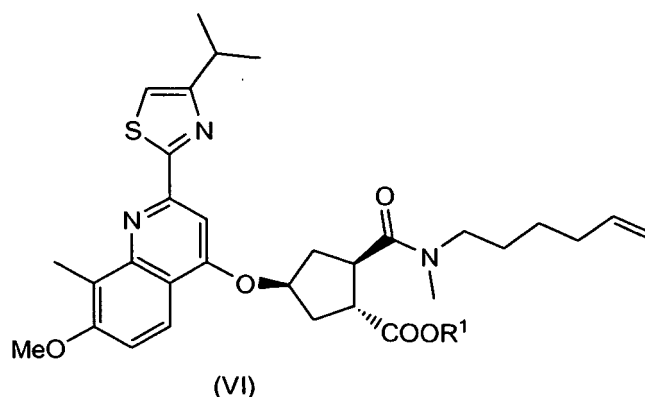
[0006] Intermediate (VI) in turn can be prepared using procedures described in WO 2008/092955, in particular starting from a hydroxycyclopentyl bis-ester of formula (Xa), by either

(a) reacting the hydroxycyclopentyl bis-ester of formula (Xa) with a thiazolyl substituted quinolinol (VII) in an ether forming reaction, thus obtaining a quinolinylthiazolyl ether derivative of formula (XII), wherein the benzyl ester group that is in cis position vis-à-vis the ether group in the quinolinylthiazolyl ether derivative of formula (XII) is selectively cleaved to a mono carboxylic acid (XI), which in turn is coupled with an alkenylamine in an amide forming reaction,

thus obtaining the desired end product of formula (VI); or

(b) selectively converting the hydroxycyclopentyl bis-ester of formula (Xa) to the mono carboxylic acid (IX), which in turn is coupled with an alkenylamine in an amide forming reaction to obtain hydroxycyclopentylamide (VIII), which in turn is reacted with a thiazolyl substituted quinolinol (VII), thus obtaining the desired end product of formula (VI); as outlined in the following reaction scheme:

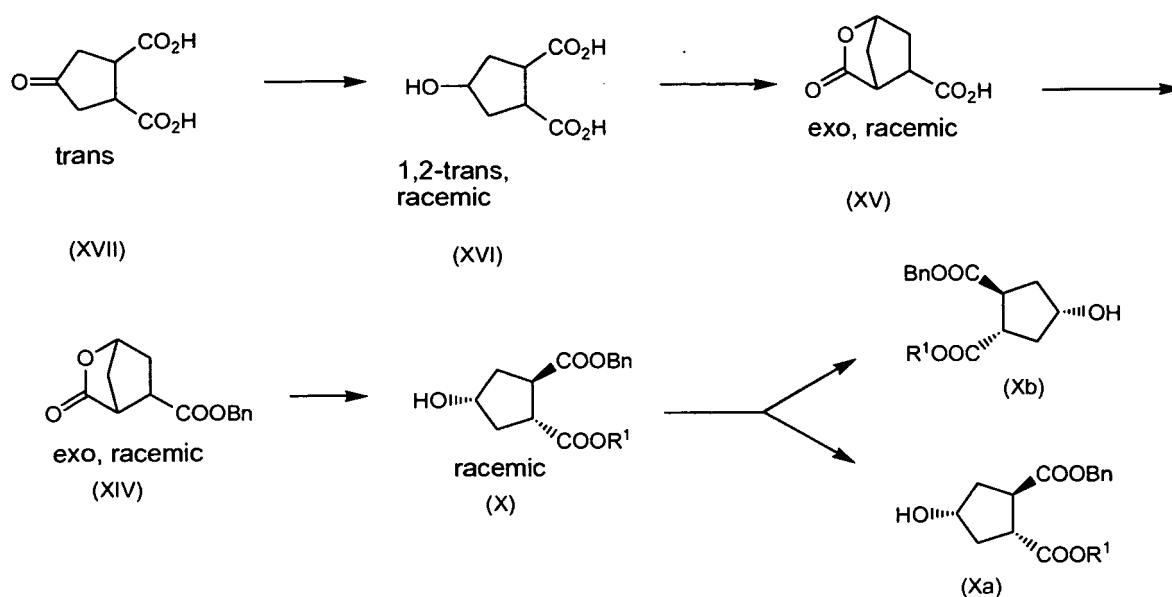




[0007] Each R¹ in the processes represented in the above scheme is as specified above and preferably R¹ is methyl. Bn represents benzyl.

[0008] The presence of various chiral centers in the compound of formula (I) and its predecessors poses particular challenges in that chiral purity is essential to have a product that is acceptable for therapeutic use. The intermediate (VI) has three chiral centers and getting the correct stereochemistry for all three centers is an important challenge for any synthesis processes aimed at preparing this compound. Hence the processes for preparing (VI) should result in products of acceptable chiral purity without use of cumbersome purification procedures with the loss of substantial amounts of undesired stereoisomeric forms.

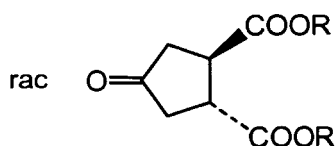
[0009] WO 2008/092955 describes a synthesis procedure for intermediate (Xa) starting from 4-oxo-cyclopentyl-1,2-bis-carboxylic acid (XVII) by reducing the keto function to an alcohol, thus obtaining 4-hydroxy-cyclopentyl-1,2-bis-carboxylic acid (XVI), which in turn is cyclized to the bicyclic lactone (XV), wherein the carboxylic acid group in the bicyclic lactone (XV) is esterified with benzyl alcohol thus obtaining the lactone benzyl ester (XIV). The lactone in the latter is opened by a transesterification reaction in the presence of a C₁₋₄alkanol, thus yielding the hydroxycyclopentyl bis-ester of formula (X), which in turn is resolved in enantiomers (Xa) and (Xb); as outlined in the following reaction scheme:



[0010] Each R¹ in the processes represented in the above scheme is as specified above and preferably R¹ is methyl.

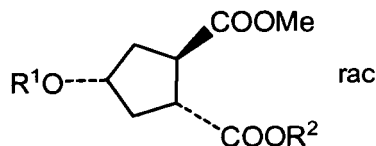
[0011] A disadvantage of the above process is that it involves a resolution of the enantiomers of (X) by chiral column chromatography, a cumbersome procedure that is difficult to run at large scale production.

[0012] Honda et al., Tetrahedron Letters, vol. 22, no. 28, pp 2679-2682, 1981, describes the synthesis of (±)-brefeldin A using the following starting materials:



2 R = H ; rac

3 R = Me ; rac



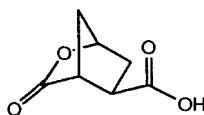
4 R¹ = H , R² = Me ; rac

5 R¹ = H , R² = CH₂C₆H₅ ; rac

6 R¹ = Ac , R² = H ; rac

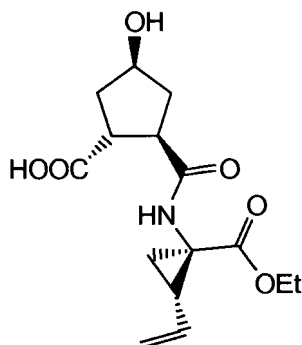
[0013] The synthesis of Honda et al. starts from *d*-trans-4-oxocyclopentane-1,2-dicarboxylic acid 2, which was esterified to the corresponding methyl ester 3, and reduced with Raney-Ni to the alcohol 4. Partial hydrolysis of 4 to the monocarboxylic acid and benzylation with benzyl bromide gave predominantly diastereoisomer 5, namely the diastereoisomer wherein the hydroxy and benzyl ester groups are in cis position. The latter ester 5 in Honda et al. and compound (X) are both racemates, but are diastereoisomers of each other, more precisely epimers on the carbon no. 4 bearing the hydroxy group. Compound (Xa) is one of the two enantiomers obtained by separation from the racemic compound (X). The other enantiomer is compound (Xb).

[0014] WO 2005/073195 describes the synthesis of enantiomerically pure bicyclic lactone (8b) starting from an enantiomer of 3,4-bis(methoxycarbonyl)cyclopentanone. The latter was prepared as described by Rosenquist et al. in Acta Chemica Scandinavica 46 (1992) 1127 - 1129. The trans (3R,4R)-3,4-bis(methoxycarbonyl)cyclopentanone isomer was converted to the bicyclic lactone (8b):



(8b)

[0015] WO 2005/073195 additionally describes further modification of lactone (8b) to the t.Bu ester, opening of the lactone and coupling with appropriately protected amino acids, e.g. with (1R,2S)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester, which in the latter instance yields:

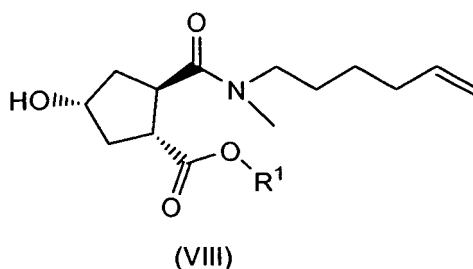


[0016] The build-up of the compounds of formula (I) necessarily involves introducing the thiazolyl substituted quinoline moiety on the cyclopentyl ring via an ether linkage. The Mitsunobu reaction offers an attractive reaction route for preparing aromatic alkylethers in which an alkyl ether is activated and reacted with a phenol. In addition, Mitsunobu reactions are in general more efficient than the O-arylation reactions, which require additional synthesis steps. In this mild reaction the stereochemistry of the alkyl part is inverted. The reaction gives rise to side products, such as R'OOC-NH-NH-COOR', wherein R' is C₁₋₄alkyl and in particular ethyl or isopropyl, other nitrogen-containing compounds, and triphenylphosphine oxide, which need to be separated from the desired end product.

[0017] The processes of the present invention are advantageous in that they are suitable for large scale production. Cumbersome purification steps, in particular by chromatography, are avoided. Essential in the synthesis of the compound of formula (I) is the built-up of the cyclopentyl moiety with the right stereochemistry at its three chiral centers.

[0018] One of the aspects of this invention concerns processes for preparing the intermediates (VIII) in high yield and purity, especially in terms of chiral purity, that are fit for large scale industrial application.

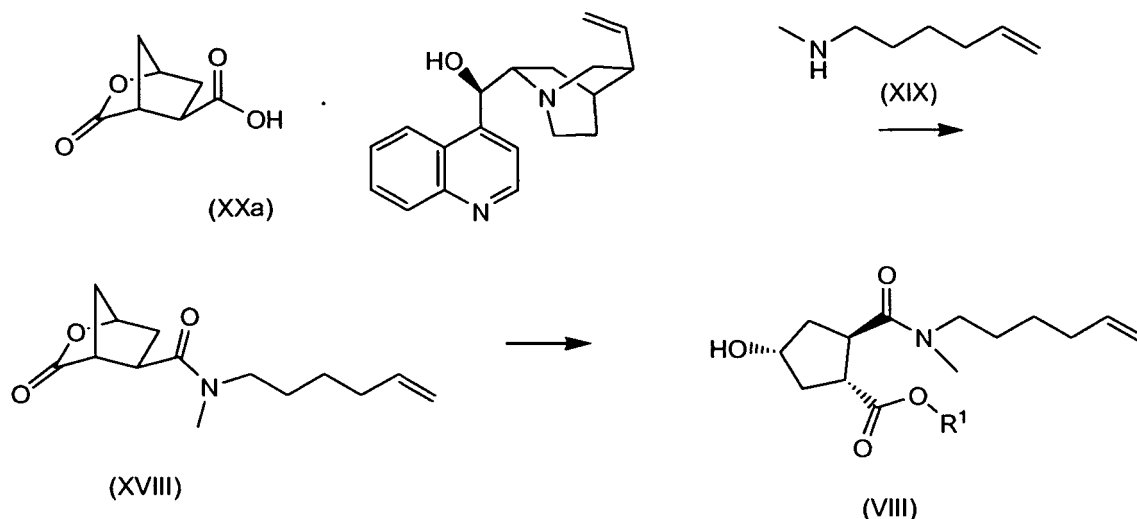
[0019] The present invention is aimed at providing procedures to prepare cyclopentyl intermediates with the right stereochemistry, in high yield and purity. In particular the present invention concerns the preparation of the intermediates



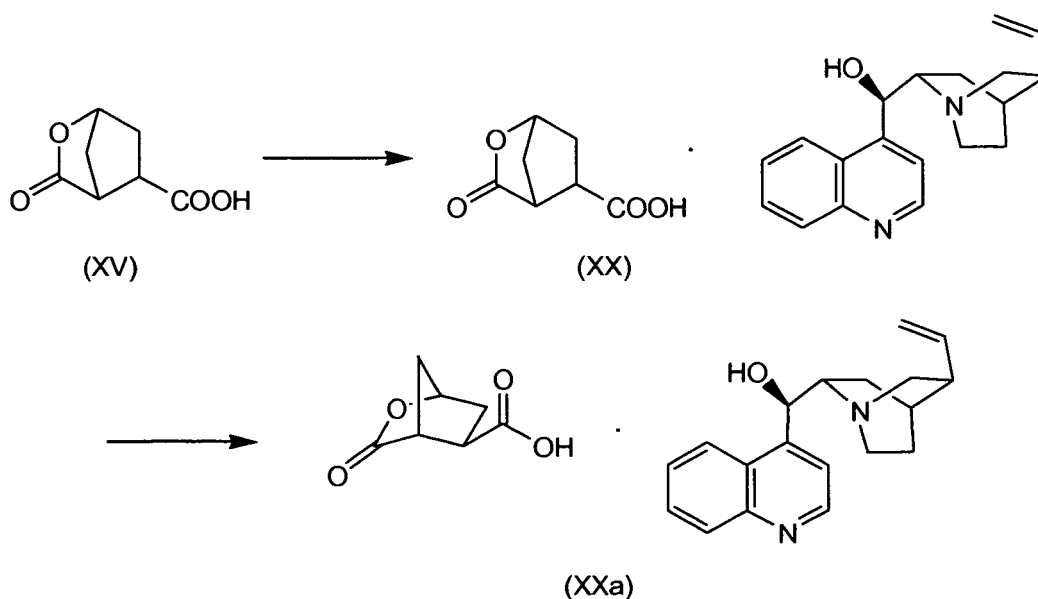
which find use in the procedures to prepare the compound of formula (I).

Description of the Invention

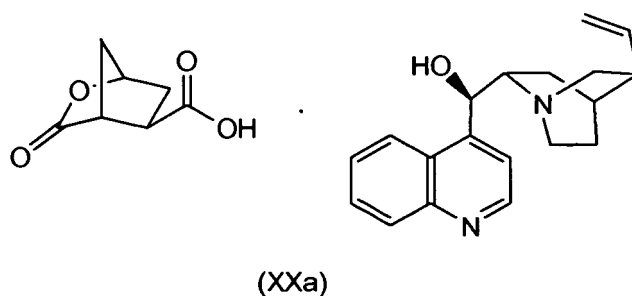
[0020] In one aspect, the present invention relates to a process for preparing a compound of formula (VIII), starting from an cinchonidine salt (XXa), which is reacted with N-methyl-hexenamine (NMHA) (XIX) in an amide-forming reaction to yield the bicyclic lactone amide (XVIII), in which the lactone group is opened to yield the desired product (VIII). These reactions are illustrated in the scheme below, wherein R¹ is as specified above.



[0021] In a further aspect the invention concerns the preparation of the cinchonidine salt (XXa), which is obtained by the resolution of the diastereoisomeric salt mixture (XX) by selective crystallization of (XXa). The salt (XX) in turn is obtained by forming the cinchonidine salt of the racemic bicyclic lactone carboxylic acid (XV), as outlined in the following reaction scheme:



[0022] In still a further aspect, the invention concerns the cinchonidine salt of formula



[0023] This salt is useful as intermediate in the preparation of intermediate (VIII), and therefore also in the preparation of the HCV inhibitor (I).

[0024] The synthesis procedures of the present invention offer the advantage that the correct stereochemistry at the cyclopentyl moiety is obtained and this without using chiral chromatography. The cinchonidine salt (XXa) has been found to selectively crystallize with high chiral purity.

[0025] The reaction of the cinchonidine salt (XXa) with NMHA (XIX) is an amide forming reaction, which comprises reacting the starting materials with an amide-coupling reagent in a reaction-inert solvent, optionally in the presence of a base. Solvents that can be used comprise halogenated hydrocarbons such as dichloromethane (DCM) or chloroform, ethers such as tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF), alcohols such as methanol or ethanol, hydrocarbon solvents such as toluene or xylene, dipolar aprotic solvents such as DMF, DMA, acetonitrile, or mixtures thereof. Preferred are dichloromethane, MeTHF, methanol, ethanol, toluene, or mixtures thereof. Amide-coupling agents comprise agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), N-isopropoxycarbonyl-2-isopropoxy-1,2-dihydroquinoline, in particular its hydrochloride salt, (IIDQ), *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (commercially available as PyBOP®), 1,1'-Carbonyldiimidazole (CDI), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDI or EDCI) as well as its hydrochloride salt, dicyclohexylcarbodiimide (DCC), or 1,3-diisopropylcarbodiimide, *O*-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluoro-phosphate (HBTU) and the like. A catalyst may be added, for example 1-hydroxybenzotriazole (HOBt) or 4-dimethylaminopyridine (DMAP). The reaction is usually conducted in the presence of a base, in particular an amine base such as a tertiary amine, e.g. triethylamine, *N*-methylmorpholine, *N,N*-diisopropylethylamine, (the latter also being referred to as Hünig's base, DIPEA, or DIEA). Preferably, no base is used. In one embodiment, the reaction is conducted in DCM or MeTHF with EEDQ, optionally with addition of methanol at the end of the reaction, at reflux temperature of the reaction mixture.

[0026] In an alternative embodiment, the salt (XXa) can be split into cinchonidine and the bicyclic lactone, and the latter can be reacted with NMHA in an amide forming reaction as described above. It has been found that the cinchonidine

salt (XXa) itself can be used in the amide forming reaction and the cinchonidine can afterwards be removed easily in the work-up of the reaction mixture, for example by treatment of the latter with an acid such as HCl, and washing away the side products with aqueous phases.

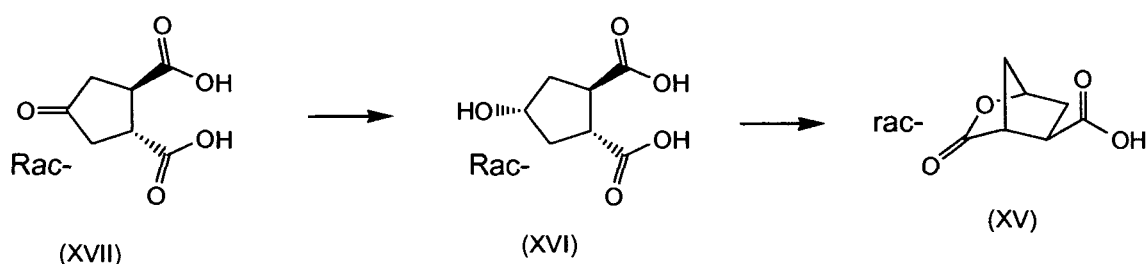
[0027] The lactone functionality in the resulting bicyclic lactone amide (XVIII) is opened by a transesterification reaction with an alcohol, which may also serve as a solvent, in particular a C₁₋₄alkanol such as methanol or ethanol, in the presence of an acid. Acids that can be used are strong organic acids such as sulfonic acids, in particular methanesulfonic acid. A solvent can be added such as an ether, in particular THF or MeTHF; or hydrocarbon solvents such as toluene or xylene. The transesterification reaction yields the ester of the alcohol that is used, e.g. when conducting the reaction in methanol, the methyl ester is formed.

[0028] The cinchonidine salt (XX) in turn can be prepared by treating the racemic bicyclic lactone carboxylic acid (XV) with cinchonidine. Typically the racemic salt (XX) is not isolated, but kept in solution while the desired isomer (XXa) is allowed to crystallize. In one embodiment, a suspension of cinchonidine is added to a solution of (XV) at slightly elevated temperature and subsequently allowing the mixture to cool whereupon the desired salt (XXa) crystallizes. Further purification may comprise recrystallization. Suitable solvents for dissolving (XV) include ester solvents such as ethyl acetate, whereas suitable solvents for the cinchonidine suspension include acetonitrile. In one embodiment the salt formation is done at a temperature of about 50 to about 70°C, in particular at about 60°C, and the mixture is allowed to cool to about room temperature, such as a temperature in the range from about 20 to about 25°C, e.g. at about 22°C. Further purification can be done by recrystallization from an appropriate solvent or solvent mixture, in particular an alcohol such as a C₁₋₄alkanol, e.g. isopropanol, or by re-slurrying in a solvent or solvent mixture, e.g. an ethanol/water mixture such as a 5%/95% (w/w) water/ethanol mixture.

[0029] The finding that the salt (XXa) can be isolated by crystallization provides an elegant way to obtain the bicyclic lactone in high enantiomeric purity. Recrystallization or reslurrying allows further purification of this salt. (XXa) can be used as a starting material in the further synthesis of intermediates (XVIII) and (VIII), as described above. The latter in turn can be converted to intermediate (VI), an important building block in the preparation of the compound of formula (I).

[0030] The racemic bicyclic lactone carboxylic acid (XV) is prepared as described in WO 2008/092955 and as outlined above in the scheme illustrating the preparation of (Xa) and (Xb). In particular, (XV) is prepared by reducing the ketocyclopentane biscalboxylic acid (XVII) to the corresponding hydroxycyclopentane biscalboxylic acid (XVI), which subsequently is converted to (XV) by lactone formation. The keto to hydroxy reduction in (XVIII) can be done by hydrogen in the presence of a noble metal catalyst, e.g. rhodium on carbon (Rh/C) or Raney Ni, in a reaction-inert solvent, e.g. in water. The resulting hydroxycyclopentane biscalboxylic acid (XVI) can be converted to a salt, e.g. a tertiary amine salt such as the triethylamine salt.

[0031] Cyclization via lactone formation of (XVII) can be done by reaction with a chloroformate, e.g. with ethyl or methyl chloroformate. This reaction is done in a reaction-inert solvent such as a ketone, in particular acetone, or an ether such as THF or MeTHF, or acetonitrile. A base can be added, e.g. a tertiary amine such as triethylamine.



[0032] In one embodiment, the present invention relates to the use of the compounds of formula (XX) or (XXa) as intermediates in the preparation of the compound of formula (I), or the salts thereof.

[0033] In another embodiment, the present invention relates to the compounds *per se* of formula (XX) or (XXa). These compounds may be in isolated form, or in solution. In particular, the compounds of formula (XX) or (XXa) are isolated in solid form.

[0034] The further processing of the compounds of formula (VIII) to the end products of formula (I) are as outlined in the reaction schemes above and in particular as outlined in WO 2008/092955. This further processing comprises a Mitsunobu reaction, which involves the inversion of the stereochemistry of the cyclopentyl carbon bearing the hydroxy group.

[0035] The intermediate of formula (VI) is crystallizable, in particular when mixed with an alcoholic solvent, more in particular when mixed with a C₁₋₄alkanol. Crystallization of the intermediate of formula (VI) allows controlling the purity of this compound as well as any compounds derived therefrom in subsequent process steps. In particular this property allows the preparation of the intermediate of formula (VI) in greater enantiomeric purity.

[0036] This crystallization of intermediate (VI) not only allows to remove the side products of the Mitsunobu reactions that yield these compounds, but also to subsequently separate intermediate (VI) from its reaction mixtures in a simple way. This separation is easily done by effecting a solvent change, in particular by adding an alcoholic solvent to the reaction mixture obtained from the Mitsunobu reactions, without having to manipulate any further the reaction mixture or any component thereof. Further, since intermediate (VI) is not soluble in an alcoholic solvent, while the by-products are, this offers immediate purification of intermediate (VI) from the reaction mixture.

[0037] As used in the foregoing and hereinafter, the following definitions apply unless otherwise noted. The term halo is generic to fluoro, chloro, bromo and iodo. The term "C₁₋₄alkyl" defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 2-methyl-2-propyl. "C₁₋₃alkyl" is generic to methyl, ethyl, 1-propyl, and 2-propyl. "C₁₋₃alkyl" is generic to methyl and ethyl. The term C₁₋₄alkanol refers to an alcohol derived from a C₁₋₄alkyl group.

[0038] The generally accepted convention for representing stereochemical compounds, which is also adhered to herein, is the following:

- A compound represented without stereobonds, e.g. compound (XV), is racemic or the configuration of the stereogenic center(s) is not defined.
- A compound represented with stereobonds and one of the descriptors "(±)", "rel", or "rac", is racemic and the stereochemistry is relative.
- A compound represented with stereobonds but without the descriptors "(±)", "rel", or "rac" refers to a non-racemic compound (scalemic substance) or an enantio-enriched, i.e. the stereochemistry is absolute.

[0039] For instance, in the Honda et al. reference the designation "(±)" is used in the title of the article, meaning that there is described a racemic synthesis with racemic intermediates. However the above convention may not necessarily be followed in all publications.

[0040] The chiral purity is given as enantiomeric ratio (e.r.). For the salts, the e.r. value refers to the ratio of the two enantiomers in the diastereomeric mixture. See for example intermediate (XV).

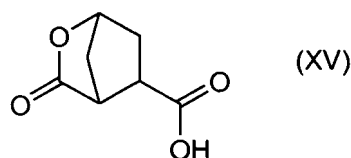
[0041] In certain embodiments, the term "about" when used in relation to a numerical value can be left out so that the exact value is meant. In other embodiments this term can mean the numerical value to which it is linked ± 10%, or ± 5%, or ± 1%.

Examples

[0042] The following examples are intended to illustrate the present invention and should not be construed as a limitation of the scope of the present invention.

Example 1

[0043]

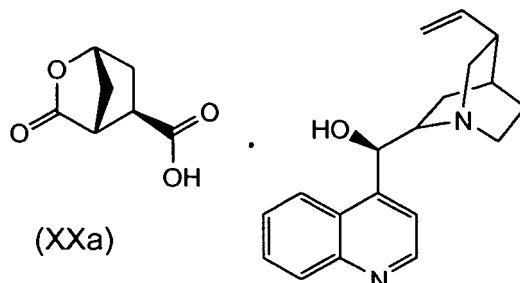


[0044] To a suspension of 32.7 g (0.19 mol) of intermediate (XVII) (racemic) in 237.5 ml water under an atmosphere of nitrogen was added 1.0 ml (0.019 mol) 50% wt/wt aqueous NaOH. Warm the mixture to 60°C and add 2.5 g Rh/C (5% wt/wt). The reaction flask was purged with hydrogen and stirred under an atmosphere of hydrogen until complete conversion was reached. The warm reaction mixture was filtered over Celite. The filter cake was washed twice with 10 ml water. Triethylamine (55.61 ml, 0.40 mol) was added and 80% of the solvent volume was distilled off under a pressure of 30 mbar. The reaction flask was fitted with a Dean-Stark trap filled with 2-methyltetrahydrofuran. 2-Methyltetrahydrofuran (100 ml) was added to the reaction mixture, which was refluxed for 4 hours to remove the remaining water. 80% of the solvent volume was distilled off under ambient pressure. The mixture was cooled to 50°C and acetone (380 ml) added. The mixture was cooled further to 22°C and again acetone (760 ml) was added. The resulting suspension was cooled under an atmosphere of nitrogen to -5°C and triethylamine (27.8 ml, 20.24 g, 0.2 mol) was added. Then ethyl chloroformate (22.68 g, 0.21 mol) was added dropwise and the mixture was stirred at 0°C for 3 hours. The reaction mixture was warmed to 22°C and stirred for a further 12 hours, then filtered over dicalite and the solids were washed

with acetone (100 ml). The resulting solution of (XV) in acetone was used in the following example to prepare its cinchonidine salt.

Example 2: Preparation of cinchonidine salt (XXa)

[0045]



Method 1

[0046] Approximately 80% of the solvent volume was distilled off under atmospheric pressure. Ethyl acetate (190 ml) was added and the organic solution was washed with aqueous HCl (2M, 114 ml), yielding a solution of (XV) in ethyl acetate. The solution of (XV) in ethyl acetate was added to a suspension of cinchonidine (55.94 g, 0.19 mol) in acetonitrile (760 ml) at 60°C. The resulting mixture was stirred at 60°C for 10 minutes and then cooled to 22°C and filtered. The solids were recrystallized from isopropanol (1500 ml) to yield after drying 24.8 g (29% yield) of a white solid. Chiral purity: e.r.: 89/11

H-NMR (DMSO-d₆ - 400 MHz), δ ppm 1.45 - 1.86 (m, 6 H), 1.93 - 2.19 (m, 3H), 2.32 (br s, 1H), 2.56 - 2.80 (m, 2H), 2.90 - 3.07 (m, 2 H), 3.12 - 3.29 (m, 1H), 3.30 - 3.52 (m, 1H), 4.93 - 5.03 (m, 3H), 5.52 (d, $J = 5.6\text{Hz}$, 1H), 5.80 - 5.89 (m, 1H), 7.5 (d, $J = 4.2\text{Hz}$, 1H), 7.6 (t, $J = 5.6\text{Hz}$, 1H), 8.0 (d, $J = 9.3\text{Hz}$, 1H), 8.3 (d, $J = 8.1\text{Hz}$, 1H), 8.8 (d, $J = 4.6\text{Hz}$, 1H),

Method 2

[0047] Approximately 80% of the solvent volume was distilled off under atmospheric pressure. Ethyl acetate (522 ml) was added and approximately 50% of the solvent volume was distilled off. The remainder was cooled to 22°C and ethyl acetate (180 ml) was added. The resulting suspension was filtered and the filtrate added to a suspension of cinchonidine (55.94 g, 0.19 mol) in acetonitrile (760 ml). This mixture was warmed to 60°C, stirred for 10 minutes, then cooled to 22°C and filtered. The solids were recrystallized from isopropanol (1500 ml) to yield after drying 24.8 g (29% yield) of a white solid. Chiral purity: e.r.: 90/10

Method 3

[0048] Following the procedure of Method 2, but changing the suspension of cinchonidine (55.94 g, 0.19 mol) in acetonitrile (760 ml) by a suspension of cinchonidine (55.94 g, 0.19 mol) in isopropanol (325 ml) and ethanol (325 ml), there were obtained 24.8 g (29%) of a white solid. Chiral purity: e.r.: 92/8.

[0049] The chemical purity of (XXa) as well as the e.r. can be increased by either recrystallisation or re-slurry of the salts, as described in the following three procedures.

[0050] 12 g of crude (XXa) (chemical purity: acid titration: 96.2%, base titration 102.2%; chiral purity: e.r.: 78.7/21.3) was dissolved in 500 ml refluxing 2-propanol. The mixture was allowed to cool slowly. If the crystallisation did not begin spontaneously, the mixture was seeded with (XXa) at 40°C, then stirred at this temperature for 2 hours. After cooling to room temperature, the mixture was stirred further for 2 hours, filtered and washed with 50 ml of 2-propanol to give, after drying in vacuum at 50°C, 5.51 g of white product. Chemical purity: acid titration 99.6%, base titration 98.4%; chiral purity: e.r.: 88.1/11.9.

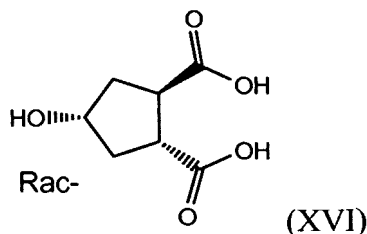
[0051] A mixture of 5.3 g (XXa) with e.r. 87.0/13.0 and 0.5 g (XXa) with e.r.: 90.6/9.4 was dissolved in 160 ml refluxing ethanol containing 5 wt % of water. The clear solution was allowed to cool slowly. If the crystallization did not begin spontaneously, the mixture was seeded with (XXa) at 45°C. After cooling to room temperature, the mixture was stirred further for 14 hours, filtered and washed with 10 ml of ethanol containing 5 wt % of water to give, after drying in vacuum at 50°C, 4.21 g of white product. Chiral purity: e.r.: 96.5/3.5

[0052] A mixture of 25 g (XXa) with e.r. 87.0/13.0 and 2.5 g (XXa) with e.r.: 90.6/9.4 was heated to reflux in 160 ml

ethanol containing 5 wt % of water. After 1 hour at reflux, the slurry was allowed to cool to room temperature over 2 hours and stirred further for 14 hours. The mixture was then filtered and washed with 15 ml of ethanol containing 5 wt % of water to give, after drying in vacuum at 50°C, 22.96 g of white product. Chiral purity: e.r.: 97.6/2.4

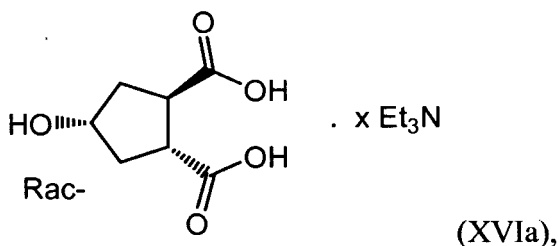
Example 3: preparation of (XVI) and its triethylamine salts (XVIa).

[0053]



(a) 344 mg (2 mmol) (XVII) and 725 mg (4 mmol) tetramethylammonium hydroxide pentahydrate were dissolved in a mixture of 2.5 ml methanol and 2.5 ml MeTHF. The solution was stirred overnight at room temperature under hydrogen atmosphere in the presence of 82 mg wet 5% rhodium on charcoal as a catalyst. The catalyst was filtered off and the filtrate was diluted to a final volume of 100 ml with methanol. LC analysis showed that 46.% (XVI) was formed as its bis(tetramethylammonium) salt while 41% (XVII) was still present as its bis(tetramethylammonium) salt.

(b) To 400g of a 6.6 wt/wt% (XVI) solution in water was added 44.4 ml triethylamine. 330 g solvent was distilled off under vacuum, then the oily residue was allowed to cool to 50°C and 51.5 ml acetone was added thus obtaining a suspension. This suspension was cooled to room temperature and 155 ml more acetone was added. The suspension was cooled to 5°C and stirred overnight at that temperature. The solid was filtered, washed with cold acetone and dried at 70°C under vacuum thus obtaining 15.05 g (XVI) as its complex with various amounts of triethylamine (XVIa) as a white crystalline powder. Yield: 37%. For example (XVI) as its complex with 1/3, or with 2 triethylamine could be obtained.



wherein x is between 1/3 and 3, e.g. x is 1/3; x is 2.

Purification of (XVIa)

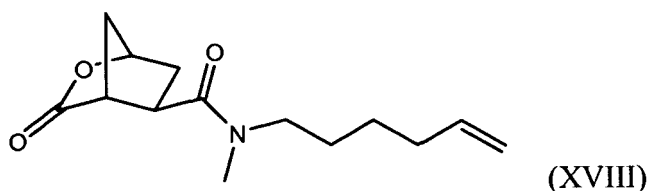
[0054]

(a) 2.00 g crude (XVIa) was suspended in 10.4 ml acetone and the suspension was brought to reflux before being allowed to cool down to room temperature. The solid was filtered, washed with acetone and dried at 50°C under vacuum to give 210 mg pure (XVIa) as a white powder. Yield: 35%.

(b) 2.00 g crude (XVIa) was suspended in 10.4 ml butanol and the suspension was brought to reflux before being allowed to cool down to room temperature. The solid was filtered, washed with acetone and dried at 50°C under vacuum to give 190 mg purified (XVIa) as a white powder. Yield: 14%.

Example 4: preparation of (XVIII)

[0055]



(a) 14.18 g (31.5 mmol) (XXa) (e.r.: 90/10), 3.92 g (34.6 mmol) NMHA and 8.56 g (34.6 mmol) EEDQ were suspended in 157 ml DCM and the resulting suspension was refluxed overnight. 47.2 ml methanol was added and the reflux was prolonged overnight. The reaction mixture was then concentrated under vacuum and the residue was partitioned between 47 ml toluene and 79 ml aqueous 1M HCl. The organic layer was successively washed with 31.5 ml water, 31.5 ml aqueous 1M NaOH and 31.5 ml water, then concentrated under vacuum to give 11.93 g crude (XVIII) (e.r. 90/10), which was used without purification in the next step.

(b) 2.50 g (5.55 mmol) (XXa), 691 mg (6.10 mmol) NMHA and 1.51 g (6.10 mmol) EEDQ were suspended in 28 ml THF and the suspension was refluxed for 2 days. 22 ml toluene was added and 28 ml solvent was distilled off. After cooling to 50-60°C, 19.4 ml aqueous 1N HCl was added and the two layers were separated. The organic layer was washed with 5.6 ml water then concentrated under vacuum and the residue was purified by flash chromatography to give 910 mg (XVIII). Yield: 65%.

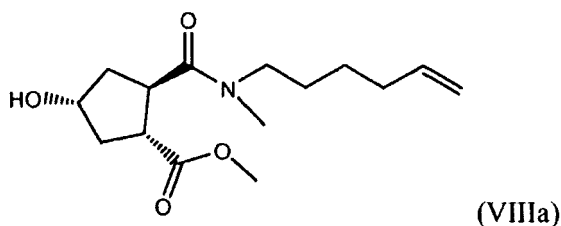
¹H NMR (CDCl₃, 600 MHz, two rotamers present, ratio 55 / 45): ppm 1.26 - 1.38 (m, 2 H), 1.43 - 1.60 (m, 2 H), 2.01 (m, 2 H), 2.07 - 2.21 (m, 4 H), 2.86 (s, 3 H - minor rotamer), 2.89 - 2.97 (m, 2 H), 2.97 (s, 3 H - major rotamer), 3.21 (ddd, 1 H - minor rotamer, J = 14.7, 9.1, 5.8 Hz), 3.29 (m, 1 H - minor rotamer), 3.31 (t, 2 H, J = 7.6 Hz - major rotamer) 4.87 - 4.93 (m, 2 H) 4.96 (d, 1 H, J = 16.2 Hz) 5.71 (m, 1 H).

¹³C NMR (CDCl₃, 150 MHz, two rotamers present): major rotamer: ppm 25.86, 26.39, 33.24, 33.94, 35.17, 37.43, 37.97, 45.71, 47.95, 80.67, 114.71, 138.26, 170.91, 177.33 - minor rotamer: ppm 25.7, 27.72, 33.14, 33.69, 34.29, 36.72, 38.02, 46.19, 49.61, 80.64, 115.22, 137.73, 171.17, 177.28.

(c) 17.85 g (39.6 mmol) (XXa) (e.r.: 97.6/2.4), 4.71 g (41.6 mmol) NMHA and 10.78 g (43.6 mmol) EEDQ were suspended in 198 ml MeTHF. The suspension was refluxed 2 days then cooled to room temperature. The solid materials (consisting mostly of cinchonidine) was filtered off and rinsed with toluene. To the combined filtrate were added 40 ml water and 7.14 ml concentrated HCl. The resulting two layers were separated and the organic one was washed with 20 ml water, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by chromatography through silica gel (eluent: ethyl acetate - heptane : 65/35) to give 9.35 g (XVIII) as an oil. Yield: 68%.

Example 5: preparation of (VIIIa), which is the intermediate of formula (VIII) wherein R¹ is methyl.

[0056]



(a) 1.05 g (4.2 mmol) (XVIII) was dissolved in 25 mL methanol. 0.014 mL (0.2 mmol) methanesulfonic acid was added and the reaction mixture was stirred three days at room temperature. The volatiles were removed under vacuum and the residue was redissolved in toluene - aqueous 0.33 M NaOH mixture 15 mL each). The layers were separated and the organic layer was dried over magnesium sulfate and concentrated under vacuum to give 330 mg crude (VIIIa) as an oil (yield: 28%).

(b) 20.0 g (44.4 mmol) (XXa), 5.53 g (48.8 mmol) NMHA and 12.08 g (48.8 mmol) EEDQ were suspended in 222 ml methanol. The mixture was refluxed for 24 hours then 178 ml toluene was added. 250 ml solvents were distilled off and the resulting suspension was cooled to 30°C. 155 ml aqueous 1M HCl was added and the two layers were

separated. The water layer was extracted twice with 44 ml toluene. The combined organic layers were dried over magnesium sulfate and filtered giving 122.78 g of 4.1 wt/wt% (VIIIa) solution in toluene. Yield: 40%.

(c) 18.42g of 4. wt/wt% (VIIIa) solution in toluene was concentrated under vacuum and the residue was purified by flash chromatography (eluent: ethyl acetate - DCM: 15/85) to give 680 mg chemically pure (VIIIa).

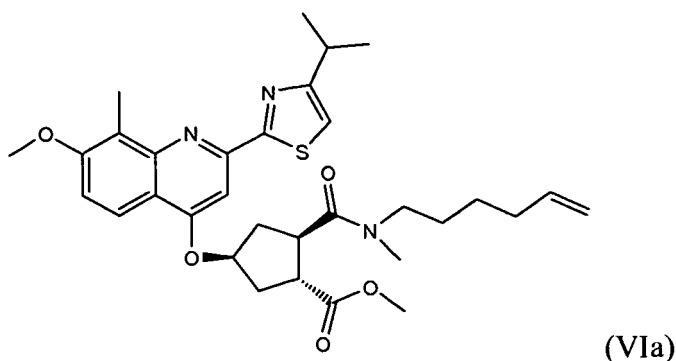
(d) 44.06 g (97.8 mmol) (XXa) (e.r.: 92.4 / 7.6), 12.18 g (107.6 mmol) NMHA and 26.60 g (107.6 mmol) EEDQ were suspended in 490 ml methanol. The mixture was refluxed overnight, then 391 ml toluene was added and 750 ml of the solvents were distilled off. 156 ml water and 30.8 ml concentrated HCl were added to the residue. The resulting two layers were separated and the water layer was extracted with 98 ml toluene, then with 98 ml MeTHF. The combined organic layers were dried over magnesium sulfate and filtered to give 384 g 3.6 wt/wt% (VIIIa) solution in MeTHF-toluene. Yield: 50%.

(e) 19 g (42.2 mmol) (XXa) (e.r.: 93.4/6.6), 5.01 g (44.3 mmol) NMHA and 11.46 g (46.4 mmol) EEDQ were suspended in 210 ml THF. The suspension was refluxed overnight, then cooled to room temperature. The solid materials (mostly cinchonidine) were filtered off and rinsed with 84 ml toluene. To the combined filtrates were added 42 ml water and 7.6 ml concentrated HCl. The two layers were separated and the organic layer was washed with 21 ml water, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in 84 ml methanol, 0.14 ml methanesulfonic acid was added and the solution was stirred overnight at room temperature, then refluxed for 24 h before being cooled to room temperature. 223 mg sodium carbonate was added and the mixture was stirred for 1 hour at room temperature. 295 ml toluene was added and 160 ml solvents were distilled off to give 184.9 g of 5.3 wt/wt% (VIIIa) solution in toluene. Yield: 82%.

(f) 19 g (42.2 mmol) (XXa) (e.r.: 93.4/6.6), 5.34 g (47.2 mmol) NMHA and 12.51 g (50.5 mmol) EEDQ were suspended in 210 ml toluene. The suspension was refluxed for 2 days, then cooled to room temperature. A quantitative analysis showed an in situ yield of 80% of (XVIII). The solid materials (mostly cinchonidine) were filtered off and rinsed with 42 ml toluene. To the combined filtrates were added 42 ml water and 7.6 ml concentrated HCl. The two layers were separated and the organic layer was washed with 21 ml water then with 21 ml brine and concentrated by distilling off 206 ml solvents. To the concentrate were added 84 ml methanol and 0.14 ml methanesulfonic acid. The resulting solution was stirred overnight at room temperature. 223 mg sodium carbonate was added and stirring was continued for an additional 1-2 hours. 295 ml toluene was added and the resulting solid materials were filtered off. 183 ml of solvents were distilled off to give 180.5 g of 2.7 wt/wt% (VIIIa) solution in toluene. Overall yield of (VIIIa): 41 %.

Example 6: preparation of (VIa), which is the intermediate of formula (VI) wherein R¹ is methyl.

[0057]

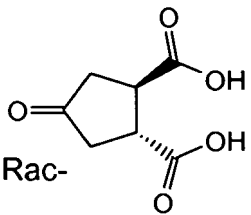
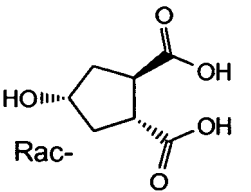
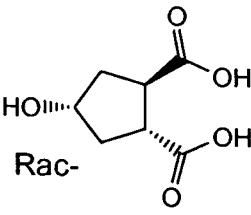
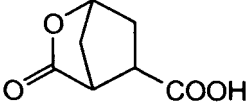


(a) 20.0 g (44.4 mmol) (XXa) (e.r.: 90.1/9.9), 5.53 g (48.8 mmol) NMHA and 12.08 g (48.8 mmol) EEDQ were suspended in 222 ml methanol. The mixture was refluxed for 24 hours, then 178 ml toluene was added. 250 ml solvents were distilled off and the resulting suspension was cooled to 30°C. 155 ml aqueous 1M HCl was added and the two layers were separated. The water layer was extracted twice with 44 ml toluene. The combined organic layers were dried over magnesium sulfate and filtered giving 122.78 g of 4.1 wt/wt% (VIIIa) solution in toluene. To 98.22 g of this solution were added 11.17 g (35.5 mmol) (VII) and 9.78 g (37.3 mmol) triphenylphosphine and the mixture was cooled to 0°C. 7.4 ml (37.3 ml) DIAD was added dropwise, then the resulting reaction mixture was stirred at 0°C for 2 hours during which a precipitate appeared. 0.1 ml acetic acid was added and the precipitate was

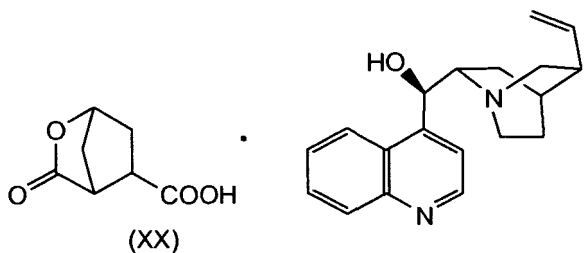
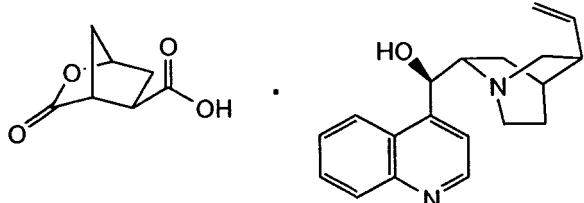
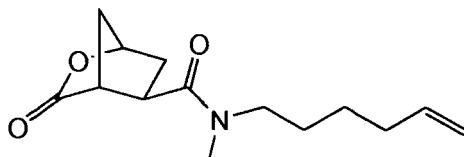
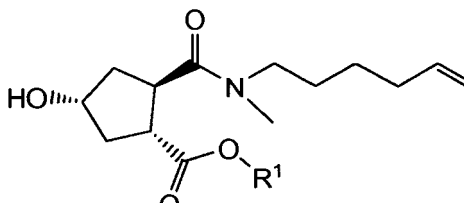
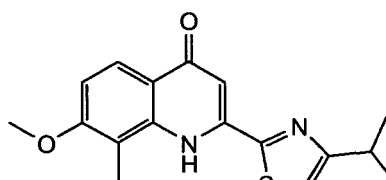
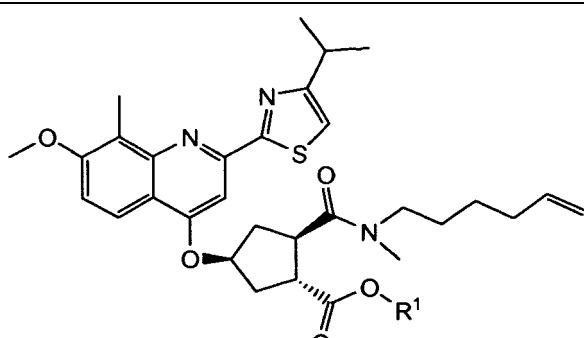
filtered off. The filtrate was concentrated under vacuum and the residue was dissolved in 71 ml boiling isopropanol. The solution was cooled to 0°C allowing (VIa) to crystallize. The solid was filtered, washed with cold isopropanol and dried under vacuum to give 6.32 g (VIa) (e.r.: 97.2/2.8). Yield from (XXa): 31%.

(b) To 382.8 g of 3.6 wt/wt% (48.6 mmol) (VIIIa) solution in MeTHF-toluene, were added 18.53 g (48.6 mmol) (VII) and 19.7 g (75.4 mmol) triphenylphosphine. 118 g of the solvents were distilled off and the resulting residue was cooled to 0°C. 14.9 ml (75.4 mmol) DIAD was added dropwise and the reaction mixture was stirred 2 hours at 0°C. The resulting solid precipitate (mostly triphenylphosphine oxide) was filtered off and washed with cold toluene. 140 g solvents were distilled off from the combined filtrates, then 97 ml 1-butanol was added and 77 g solvents were distilled off. The mixture was cooled to 80°C and 97 ml isopropanol and 2.43 g dicalite were added. After stirring a few minutes at reflux, the mixture was filtered while hot and the resulting filtrate was cooled to 40°C. 14 mg (VIa) was added as seeding material and the mixture was cooled to 0°C. After stirring overnight at 0°C, 48 ml isopropanol was added and stirring was continued at 0°C for 2 hours. (VIa) was isolated by filtration, washed with 9.7 ml cold isopropanol and dried at 70°C under vacuum. A first portion of 8.77 g (VIa) was obtained (yield: 28%). The mother-liquors were concentrated under vacuum and the residue was purified by flash chromatography through silicagel to yield a second crop of (VIa) (12.1 g - yield: 43%).

(c) To 58.9 g (8.3 mmol) of 4 wt/wt% (VIIIa) solution in toluene, were added 2.86 g (9 mmol) (VII) and 2.29 g (10.2 mmol) triphenylphosphine. The suspension was dried by distilling off 27 ml solvent, then cooled to 0°C. 8.7 ml (10.2 mmol) DIAD was added dropwise and the reaction mixture was stirred 1-2 hour at 0°C. The solid materials were filtered off and rinsed with 4.2 ml toluene. From the combined filtrates, 27 ml solvent were distilled off. 25 ml 1-butanol was added and 25 ml solvents were distilled off. The residue was cooled to 80°C, 25 ml isopropanol and 415 mg dicalite were added, the suspension was refluxed and filtered while hot. The filtrate was cooled to 30°C and 2.4 mg (VIa) was added as seeding material. The suspension was cooled to 0°C and stirred at this temperature overnight. (VIa) was filtered, washed with 2.5 ml cold isopropanol and dried under vacuum, thus obtaining 24.3 g white powder. Yield: 80%.

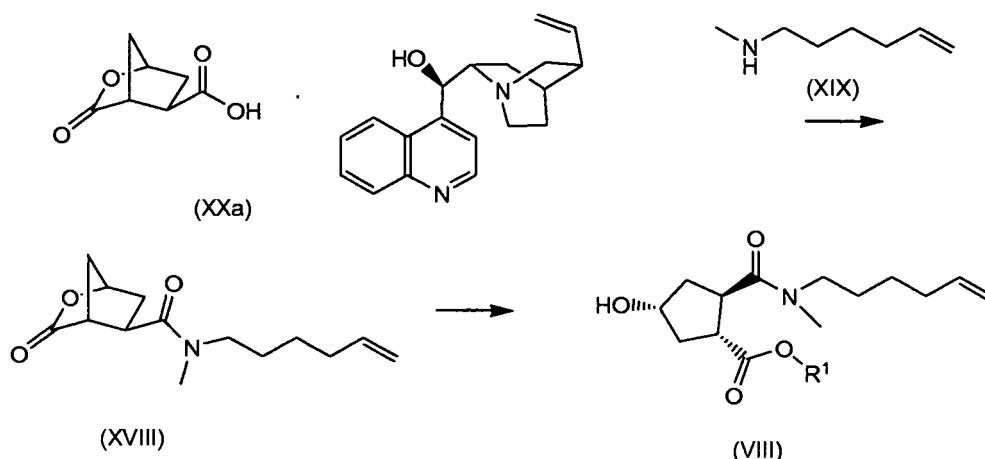
Structure	Formula no.
 Rac-	(XVII)
 Rac-	(XVI)
 Rac-	. x Et ₃ N x = 1/3 to 3 (XVIa)
 (XV)	(XV)

(continued)

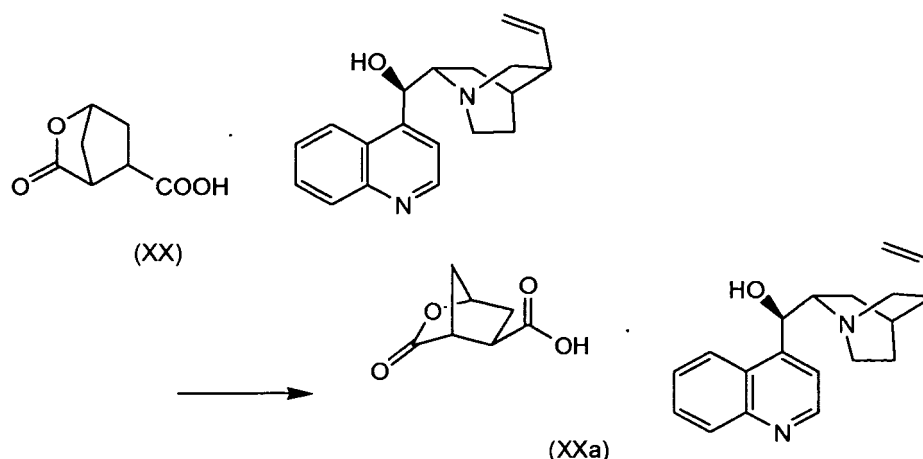
Structure	Formula no.
 <p>(XX)</p>	(XX)
 <p>(XXa)</p>	(XXa)
 <p>(XVIII)</p>	(XVIII)
 <p>(VIII)</p> <p>(VIIIa): R¹ = CH₃</p>	(VIII)
 <p>(VII)</p>	(VII)
 <p>(VI)</p> <p>(VIa): R¹ = CH₃</p>	(VI)

Claims

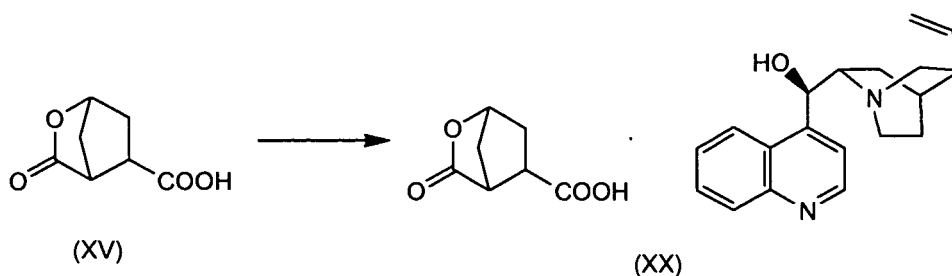
1. A process for preparing a compound of formula (VIII), starting from a cinchonidine salt (XXa), which is reacted with N-methyl-hexenamine (NMHA) (XIX) in an amide-forming reaction to yield the bicyclic lactone amide (XVIII), in which the lactone group is opened to yield the desired product (VIII), as illustrated in the scheme below, wherein R¹ is C₁₋₄alkyl:



2. The process of claim 1 wherein R¹ is methyl.
3. The process of claims 1 or 2, wherein amide-forming reaction is conducted in the presence of an amide-coupling reagent in a reaction-inert solvent.
4. A process as claimed in claim 3, wherein the reaction is conducted in the presence of a base.
5. The process of claim 3 or claim 4 wherein the solvent comprises halogenated hydrocarbons, ethers, alcohols, hydrocarbon solvents, dipolar aprotic solvents, or mixtures thereof.
6. The process of claim 5 wherein the halogenated solvents are dichloromethane (DCM) or chloroform, the ethers are tetrahydrofuran (THF) or 2-methyltetrahydrofuran (MeTHF), the alcohols are methanol or ethanol, the hydrocarbon solvents are toluene or xylene, the dipolar aprotic solvents are DMF, DMA, acetonitrile.
7. The process of claim 3 or claim 4 wherein the amide forming agent comprises agents N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), N-isopropoxycarbonyl-2-isopropoxy-1,2-dihydroquinoline (IIDQ), *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, CDI, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) or its hydrochloride, dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide, or O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate (HBTU).
8. The process of claim 7 wherein the amide forming agent is in the presence of a catalyst.
9. The process of claim 8 wherein the catalyst is 1-hydroxybenzotriazole (HOBt) or 4-dimethylaminopyridine (DMAP).
10. The process of claim 4 wherein the base is a tertiary amine.
11. The process of claim 10, wherein the tertiary amine is triethylamine, N-methylmorpholine, N,N-diisopropylethylamine.
12. A process for preparing the cinchonidine salt (XXa), which is obtained from the racemic salt (XX) by crystallization:



13. The process of claim 12, wherein the racemic salt (XX) is obtained by contacting the bicyclic lactone carboxylic acid (XV) with cinchonidine:



14. The process of claim 13, wherein a suspension of cinchonidine is added to a solution of (XV) at a temperature of about 50 to about 70°C and subsequently allowing the mixture to cool whereupon the desired product (XXa) crystallizes.

15. The process of claim 13, wherein (XV) is dissolved in a solvent selected from ester solvents, and solvents for the cinchonidine suspension include acetonitrile.

16. The process of claim 15, wherein the ester solvents are ethyl acetate.

17. The process of claims 14 or 15, wherein the salt formation is done at a temperature of about 60°C, and the mixture is allowed to cool to about room temperature.

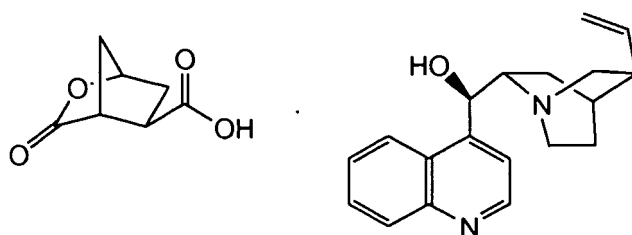
18. The process of claim 17, wherein the mixture is allowed to cool to a temperature in the range from about 20 to about 25°C.

19. The process of claims 14 or 15, wherein the salt is further purified by recrystallization from an appropriate solvent or solvent mixture; or by re-slurrying in a solvent or solvent mixture.

20. The process of claim 19, wherein the solvent in the recrystallization is a C₁₋₄alkanol, or in the re-slurrying the solvent or solvent mixture is an ethanol/water mixture.

21. The process of claim 20, wherein the C₁₋₄alkanol is isopropanol and/or the ethanol/water mixture is a 5%/95% (w/w) water/ethanol mixture.

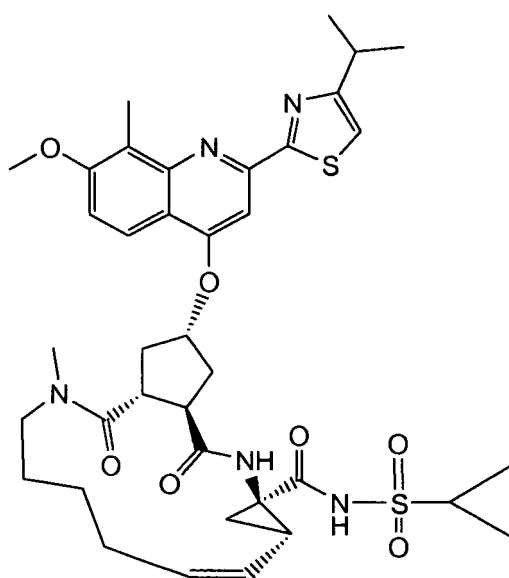
22. The cinchonidine salt of formula



(XXa)

23. The use of the chinchonidine salt (XXa) defined in claim 22, as an intermediate in the preparation of intermediate (VIII).

24. A process for the preparation of a compound of formula (I)

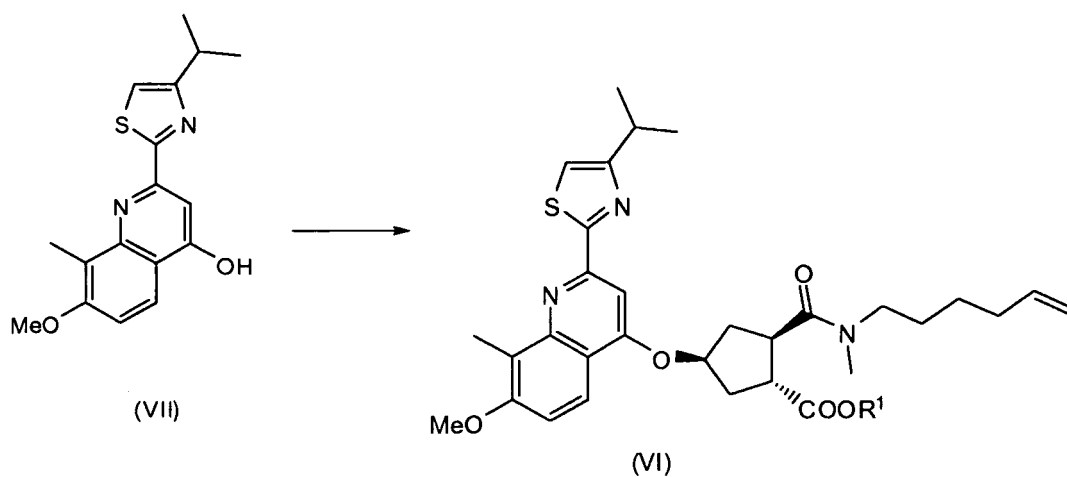


(I)

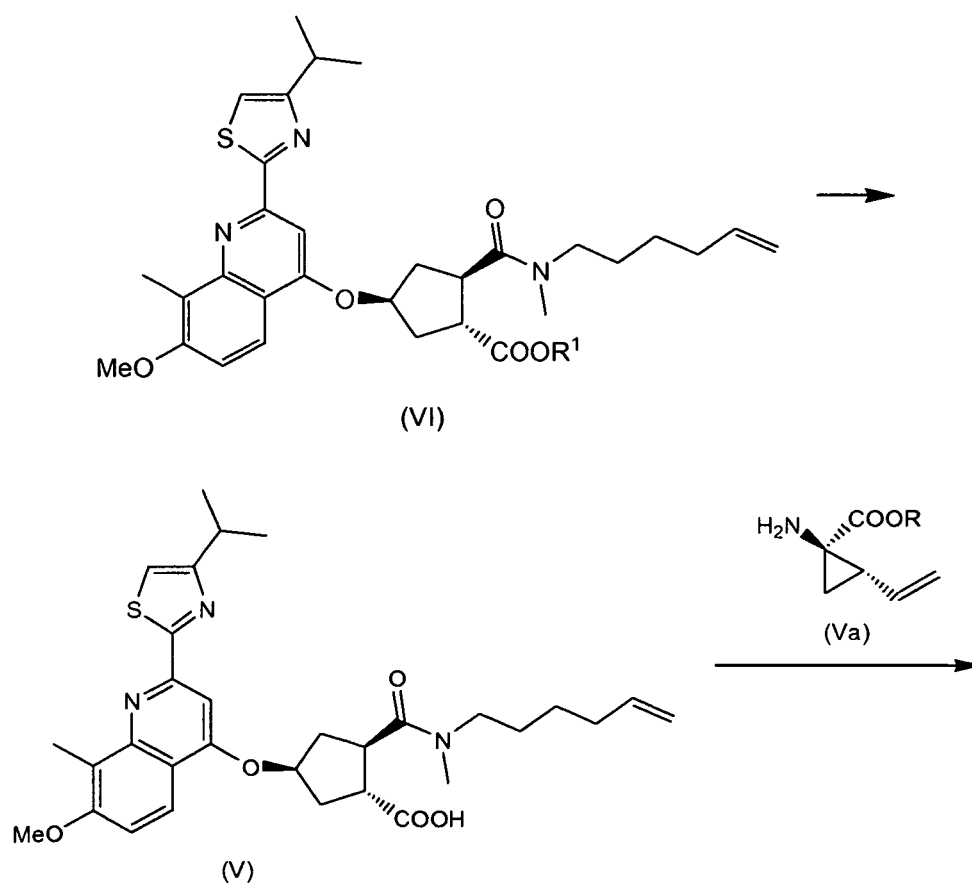
which process comprises a process for the preparation of a compound of formula (VIII) as claimed in any one of claims 1 to 11, followed by conversion to a compound of formula (I).

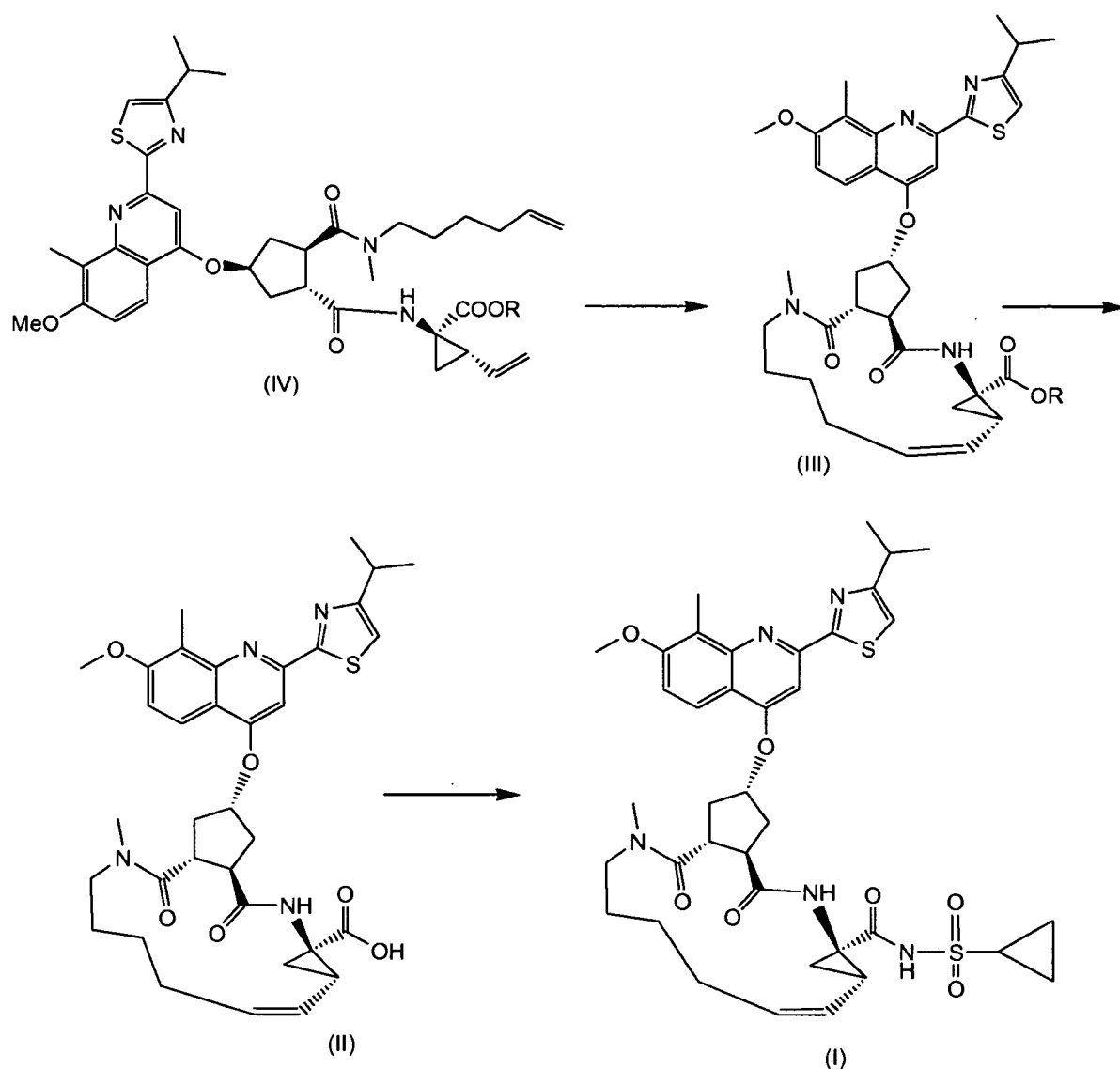
25. A process as claimed in claim 24, wherein the conversion to the compound of formula (I) is as follows:

(i) reaction of compound of formula (VIII) with a compound of formula (VII) to form a compound of formula (VI),



(ii) conversion of (VI) to (I) in accordance with the following scheme:

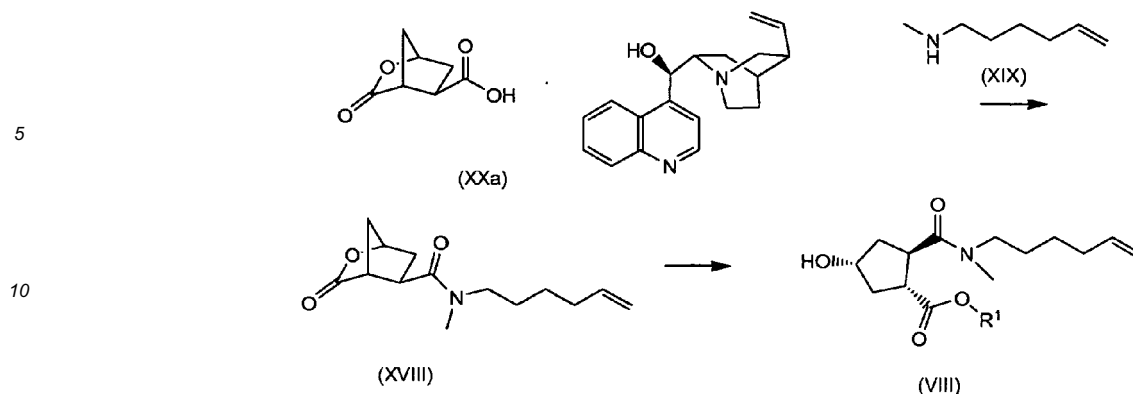




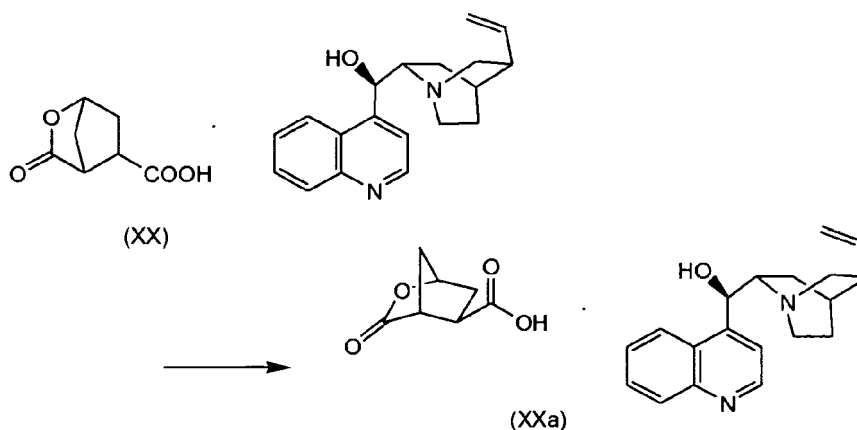
26. A process for the preparation of a compound of formula (I), as defined in claim 24, which process comprises a process for the preparation of a compound of formula (XXa) as claimed in any one of claims 12 to 21, followed by conversion to a compound of formula (I).
27. A process as claimed in claim 26, wherein the compound of formula (XXa) is first converted to a compound of formula (VIII) following a process as claimed in any one of claims 1 to 11.
28. A process as claimed in claim 27, wherein the conversion from the compound of formula (VIII) to the compound of formula (I) is as claimed in claim 25.
29. The use of the chinochonidine salt (XXa) defined in claim 22, as an intermediate in the preparation of compound (I) as defined in claim 24.

Patentansprüche

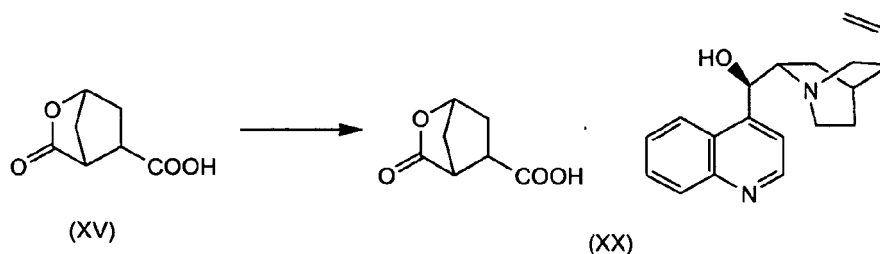
1. Verfahren zur Herstellung einer Verbindung der Formel (VIII) ausgehend von einem Cinchonidinsalz (XXa), das mit N-Methylhexenamin (NMHA) (XIX) in einer Amidbildungsreaktion zu dem bicyclischen Lactonamid (XVIII) umgesetzt wird, in dem die Lactongruppe geöffnet wird, was das gewünschte Produkt (VIII) ergibt, wie im nachstehenden Schema veranschaulicht, wobei R¹ für C₁₋₄-Alkyl steht:



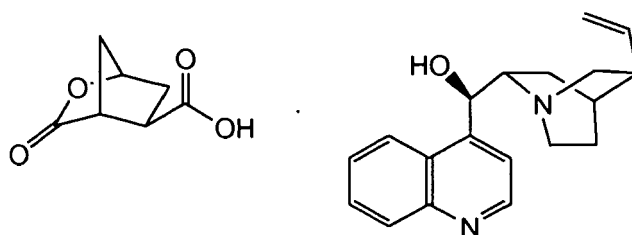
- 15 2. Verfahren nach Anspruch 1, bei dem R¹ für Methyl steht.
3. Verfahren nach Anspruch 1 oder 2, bei dem die Amidbildungsreaktion in Gegenwart eines Amidkupplungsreagens in einem unter den Reaktionsbedingungen inerten Lösungsmittel durchgeführt wird.
- 20 4. Verfahren nach Anspruch 3, bei dem die Reaktion in Gegenwart einer Base durchgeführt wird.
5. Verfahren nach Anspruch 3 oder Anspruch 4, bei dem das Lösungsmittel halogenierte Kohlenwasserstoffe, Ether, Alkohole, Kohlenwasserstoff-Lösungsmittel, dipolare aprotische Lösungsmittel oder Mischungen davon umfasst.
- 25 6. Verfahren nach Anspruch 5, bei dem es sich bei den halogenierten Lösungsmitteln um Dichlormethan (DCM) oder Chloroform handelt, es sich bei den Ethern um Tetrahydrofuran (THF) oder 2-Methyltetrahydrofuran (MeTHF) handelt, es sich bei den Alkoholen um Methanol oder Ethanol handelt, es sich bei den Kohlenwasserstoff-Lösungsmitteln um Toluol oder Xylol handelt, es sich bei den dipolaren aprotischen Lösungsmitteln um DMF, DMA, Acetonitril handelt.
- 30 7. Verfahren nach Anspruch 3 oder Anspruch 4, bei dem das Amidbildungsmittel N-Ethoxycarbonyl-2-ethoxy-1,2-dihydrochinolin (EEDQ), N-Isopropoxycarbonyl-2-isopropoxy-1,2-dihydrochinolin (IIDQ), N,N,N',N'-Tetramethyl-O-(7-azabenzotriazol-1-yl)-uroniumhexafluorophosphat (HATU), Benzotriazol-1-yloxy-tris-pyrrolidino-phosphoniumhexafluorophosphat, CDI, 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimid (EDCI) oder dessen Hydrochlorid, Dicyclohexylcarbodiimid (DCC), 1,3-Diisopropylcarbodiimid oder O-Benzotriazol-N,N,N',N'-tetra-methyluroniumhexafluorophosphat (HBTU) umfasst.
- 35 8. Verfahren nach Anspruch 7, bei dem das Amidbildungsmittel in Gegenwart eines Katalysators vorliegt.
- 40 9. Verfahren nach Anspruch 8, bei dem es sich bei dem Katalysator um 1-Hydroxybenzotriazol (HOBt) oder 4-Dimethylaminopyridin (DMAP) handelt.
10. Verfahren nach Anspruch 4, bei dem es sich bei der Base um ein tertiäres Amin handelt.
- 45 11. Verfahren nach Anspruch 10, bei dem es sich bei dem tertiären Amin um Triethylamin, N-Methylmorpholin, N,N-Diisopropylethylamin handelt.
12. Verfahren zur Herstellung des Cinchonidinsalzes (XXa), das aus dem racemischen Salz (XX) durch Kristallisation erhalten wird:
- 50



13. Verfahren nach Anspruch 12, bei dem das racemische Salz (XX) durch Inberührungbringen der bicyclischen Lactoncarbonsäure (XV) mit Cinchonidin erhalten wird:



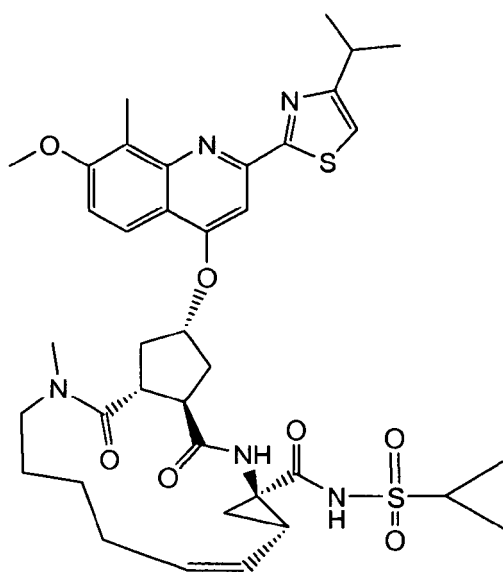
14. Verfahren nach Anspruch 13, bei dem eine Lösung von (XV) bei einer Temperatur von etwa 50 bis etwa 70°C mit einer Suspension von Cinchonidin versetzt wird und die Mischung anschließend abkühlen gelassen wird, wobei das gewünschte Produkt (XXa) kristallisiert.
15. Verfahren nach Anspruch 13, bei dem (XV) in einem aus Ester-Lösungsmitteln ausgewählten Lösungsmittel gelöst wird und Lösungsmittel für die Cinchonidinsuspension Acetonitril einschließen.
16. Verfahren nach Anspruch 15, bei dem es sich bei den Ester-Lösungsmitteln um Essigsäureethylester handelt.
17. Verfahren nach Anspruch 14 oder 15, bei dem die Salzbildung bei einer Temperatur von etwa 60°C durchgeführt wird und die Mischung auf etwa Raumtemperatur abkühlen gelassen wird.
18. Verfahren nach Anspruch 17, bei dem die Mischung auf eine Temperatur im Bereich von etwa 20 bis etwa 25°C abkühlen gelassen wird.
19. Verfahren nach Anspruch 14 oder 15, bei dem das Salz durch Umkristallisation aus einem entsprechenden Lösungsmittel oder Lösungsmittelgemisch oder durch Wiederaufschäumen in einem Lösungsmittel oder Lösungsmittelgemisch weiter gereinigt wird.
20. Verfahren nach Anspruch 19, bei dem es sich bei dem Lösungsmittel bei der Umkristallisation um ein C₁₋₄-Alkanol handelt oder es sich beim Wiederaufschäumen bei dem Lösungsmittel oder Lösungsmittelgemisch um ein Ethanol/Wasser-Gemisch handelt.
21. Verfahren nach Anspruch 20, bei dem es sich bei dem C₁₋₄-Alkanol um Isopropanol handelt und/oder es sich bei dem Ethanol/Wasser-Gemisch um ein Gemisch aus 5 Gew.-% Wasser und 95 Gew.-% Ethanol handelt.
22. Cinchonidinsalz der Formel



(XXa)

23. Verwendung des Cinchonidinsalzes der Formel (XXa) gemäß Anspruch 22 als Zwischenprodukt bei der Herstellung von Zwischenprodukt (VIII).

24. Verfahren zur Herstellung einer Verbindung der Formel (I)

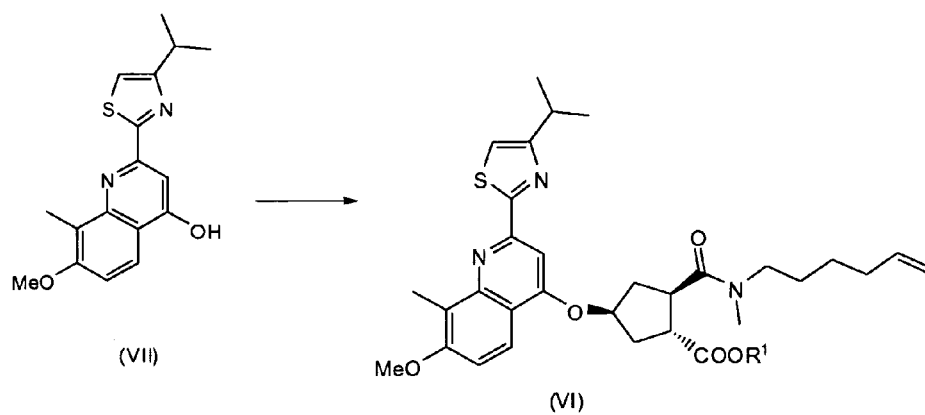


(I)

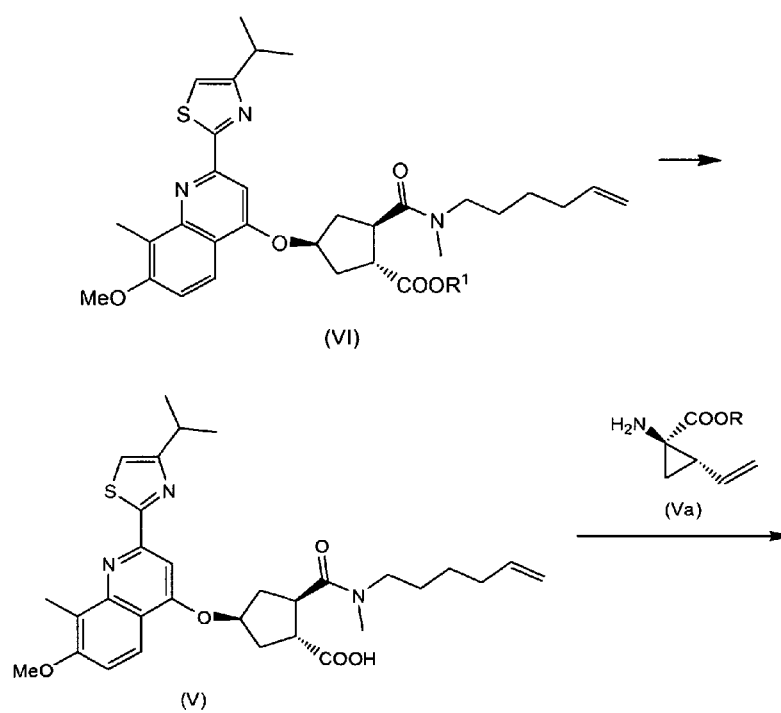
das ein Verfahren zur Herstellung einer Verbindung der Formel (VIII) nach einem der Ansprüche 1 bis 11 gefolgt von der Umwandlung in eine Verbindung der Formel (I) umfasst.

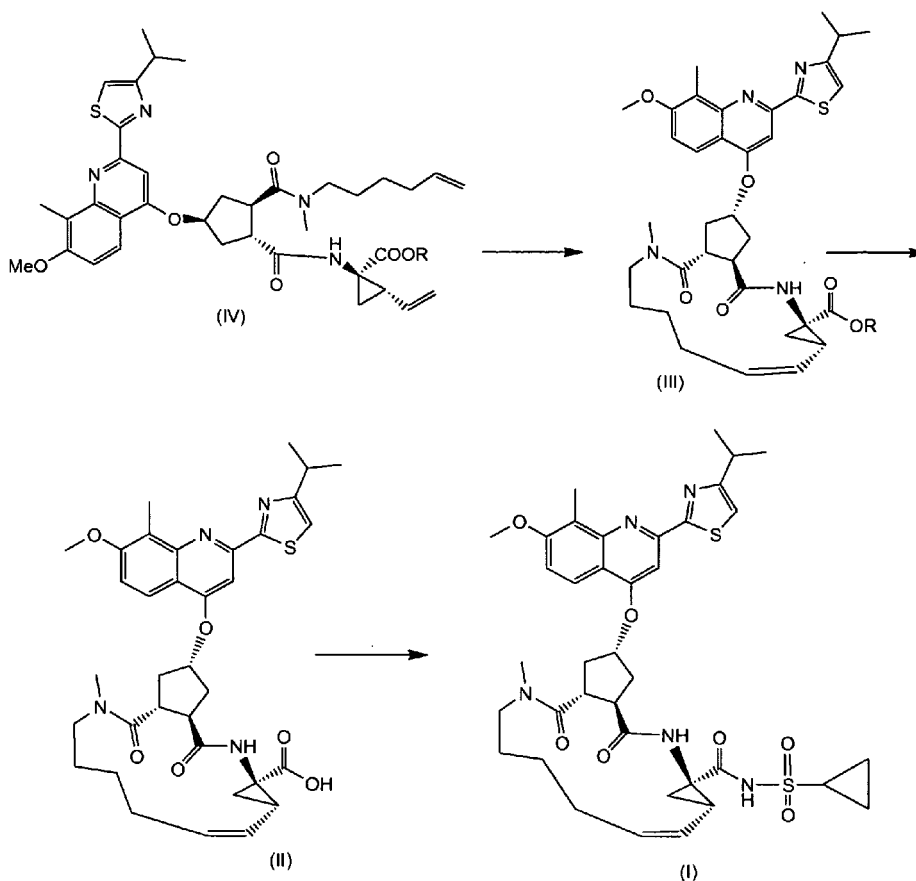
25. Verfahren nach Anspruch 24, bei dem die Umwandlung in die Verbindung der Formel (I) folgendermaßen erfolgt:

(i) Umsetzen einer Verbindung der Formel (VIII) mit einer Verbindung der Formel (VII) zu einer Verbindung der Formel (VI),



(ii) Umwandeln von (VI) in (I) gemäß dem folgenden Schema:

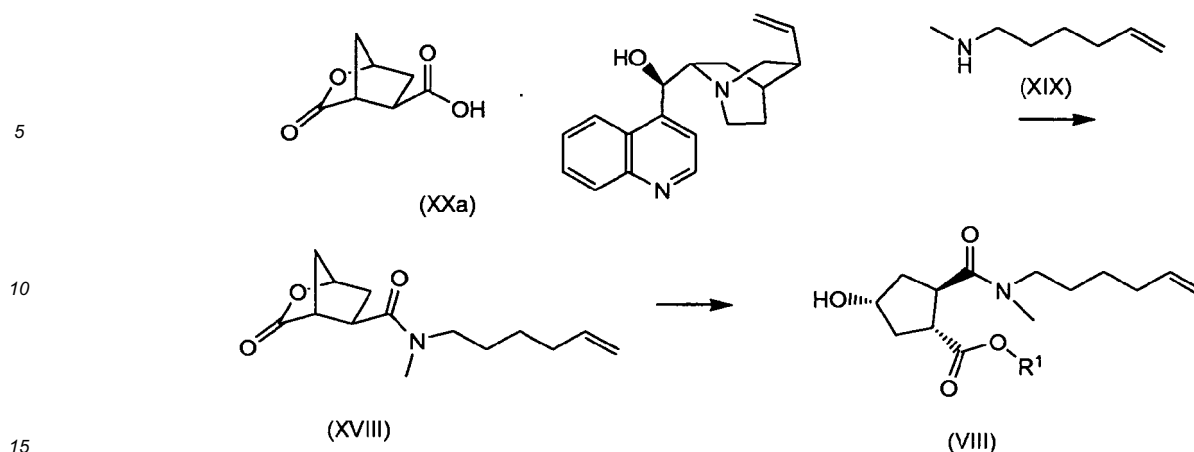




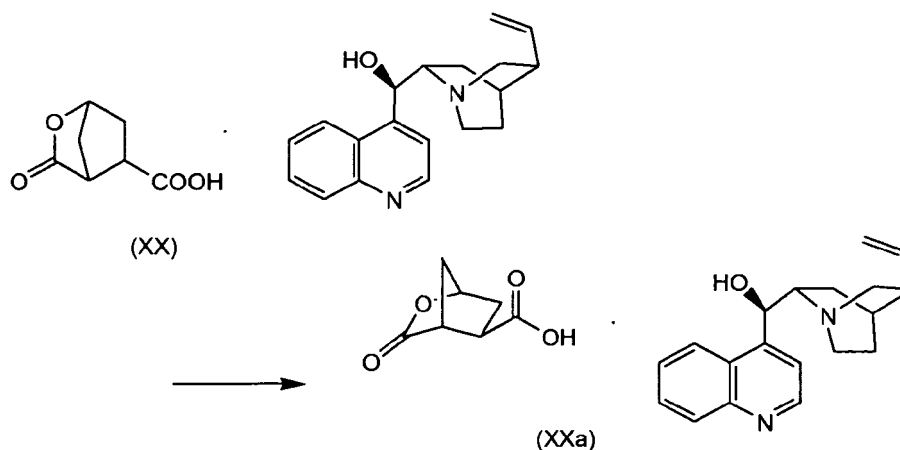
26. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 24, das ein Verfahren zur Herstellung einer Verbindung der Formel (XXa) gemäß einem der Ansprüche 12 bis 21 gefolgt von der Umwandlung in eine Verbindung der Formel (I) umfasst.
27. Verfahren nach Anspruch 26, bei dem die Verbindung der Formel (XXa) zunächst nach einem Verfahren nach einem der Ansprüche 1 bis 11 in eine Verbindung der Formel (VIII) umgewandelt wird.
28. Verfahren nach Anspruch 27, bei dem die Umwandlung der Verbindung der Formel (VIII) in die Verbindung der Formel (I) nach Anspruch 25 erfolgt.
29. Verwendung des Cinchonidinsalzes (XXa) gemäß Anspruch 22 als Zwischenprodukt bei der Herstellung von Verbindung (I) gemäß Anspruch 24.

Revendications

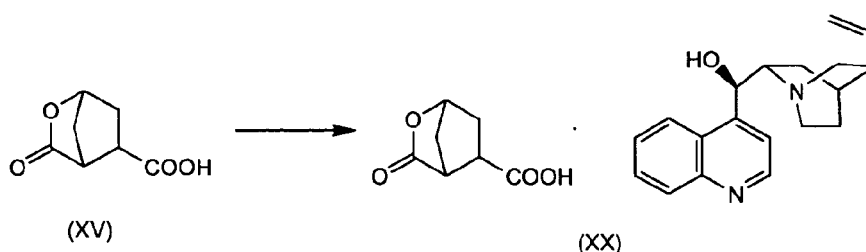
1. Procédé de préparation d'un composé de formule (VIII), en partant d'un sel de cinchonidine (XXa), qui est mis en réaction avec de la N-méthyl-hexénamine (NMHA) (XIX) dans une réaction de formation d'amide pour donner l'amide de lactone bicyclique (XVIII), dans lequel le groupement lactone est ouvert pour donner le produit désiré (VIII), comme illustré dans le schéma ci-dessous, dans lequel R^1 est C_{1-4} alkyle :



2. Procédé selon la revendication 1, **caractérisé en ce que** R¹ est méthyle.
3. Procédé selon la revendication 1 ou 2, **caractérisé en ce que** la réaction de formation d'amide est effectuée en présence d'un réactif de couplage d'amide dans un solvant inerte vis-à-vis de la réaction.
4. Procédé selon la revendication 3, **caractérisé en ce que** la réaction est effectuée en présence d'une base.
5. Procédé selon la revendication 3 ou la revendication 4, **caractérisé en ce que** le solvant comprend des hydrocarbures halogénés, des éthers, des alcools, des solvants hydrocarbonés, des solvants aprotiques dipolaires, ou des mélanges de ceux-ci.
6. Procédé selon la revendication 5, **caractérisé en ce que** les solvants halogénés sont le dichlorométhane (DCM) ou le chloroforme, les éthers sont le tétrahydrofurane (THF) ou le 2-méthyltétrahydrofurane (MeTHF), les alcools sont le méthanol ou l'éthanol, les solvants hydrocarbonés sont le toluène ou le xylène, les solvants aprotiques dipolaires sont le DMF, le DMA, l'acétonitrile.
7. Procédé selon la revendication 3 ou la revendication 4, **caractérisé en ce que** l'agent de formation d'amide comprend les agents N-éthoxycarbonyl-2-éthoxy-1,2-dihydroquinoléine (EEDQ), N-isopropoxycarbonyl-2-isopropoxy-1,2-dihydroquinoléine (IIDQ), hexafluorophosphate de N,N,N',N'-tétraméthyl-O-(7-azabenzotriazol-1-yl)uronium (HATU), hexafluorophosphate de benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium, CDI, 1-éthyl-3-(3-di-méthylaminopropyl)carbodiimide (EDCI) ou son chlorhydrate, dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide, ou hexafluorophosphate d'O-benzotriazole-N,N,N',N'-tétraméthyl-uronium (HBTU).
8. Procédé selon la revendication 7, **caractérisé en ce que** l'agent de formation d'amide est en présence d'un catalyseur.
9. Procédé selon la revendication 8, **caractérisé en ce que** le catalyseur est le 1-hydroxybenzotriazole (HOBt) ou la 4-diméthylaminopyridine (DMAP).
10. Procédé selon la revendication 4, **caractérisé en ce que** la base est une amine tertiaire.
11. Procédé selon la revendication 10, **caractérisé en ce que** l'amine tertiaire est la triéthylamine, la N-méthylmorpholine, la N,N-diisopropyléthylamine.
12. Procédé de préparation du sel de cinchonidine (XXa), qui est obtenu à partir du sel racémique (XX) par cristallisation :



13. Procédé selon la revendication 12, **caractérisé en ce que** le sel racémique (XX) est obtenu par la mise en contact de l'acide lactone carboxylique bicyclique (XV) avec la cinchonidine :



14. Procédé selon la revendication 13, **caractérisé en ce qu'on** ajoute une suspension de cinchonidine à une solution (XV) à une température d'environ 50 à environ 70°C et en laissant ensuite le mélange refroidir, après quoi le produit désiré (XXa) se cristallise.

15. Procédé selon la revendication 13, **caractérisé en ce qu'on** dissout (XV) dans un solvant choisi parmi les solvants esters, et les solvants pour la suspension de cinchonidine incluent l'acétonitrile.

16. Procédé selon la revendication 15, **caractérisé en ce que** les solvants esters sont l'acétate d'éthyle.

17. Procédé selon la revendication 14 ou 15, **caractérisé en ce que** la formation de sels est réalisée à une température inférieure à environ 60°C, et on laisse le mélange refroidir à environ la température ambiante.

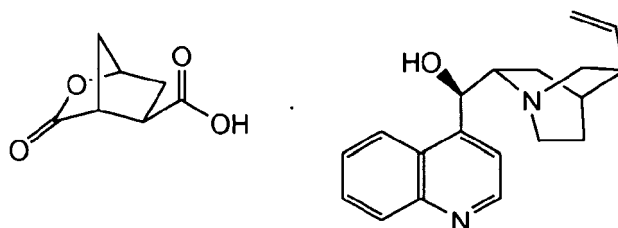
18. Procédé selon la revendication 17, **caractérisé en ce qu'on** laisse le mélange refroidir à une température dans la gamme comprise entre environ 20 et environ 25°C.

19. Procédé selon la revendication 14 ou 15, **caractérisé en ce que** le sel est purifié de nouveau par recristallisation dans un solvant approprié ou un mélange de solvants ; ou par ré-empâtage dans un solvant ou mélange de solvants.

20. Procédé selon la revendication 19, **caractérisé en ce que** le solvant dans la recristallisation est un C₁₋₄alcanol, ou dans le ré-empâtage le mélange ou le mélange de solvants est un mélange éthanol/eau.

21. Procédé selon la revendication 20, **caractérisé en ce que** le C₁₋₄alcanol est l'isopropanol et/ou le mélange éthanol/eau est un mélange eau/éthanol 5 %/95 % (p/p).

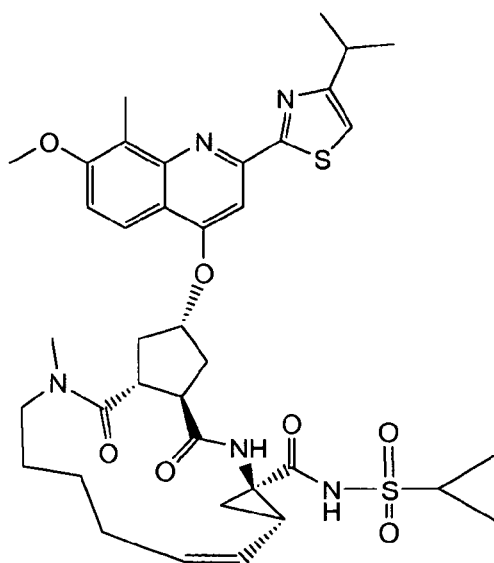
22. Sel de cinchonidine de formule



(XXa)

23. Utilisation du sel de cinchonidine (XXa) défini dans la revendication 22, en tant qu'intermédiaire dans la préparation de l'intermédiaire (VIII).

24. Procédé de préparation d'un composé de formule (I)

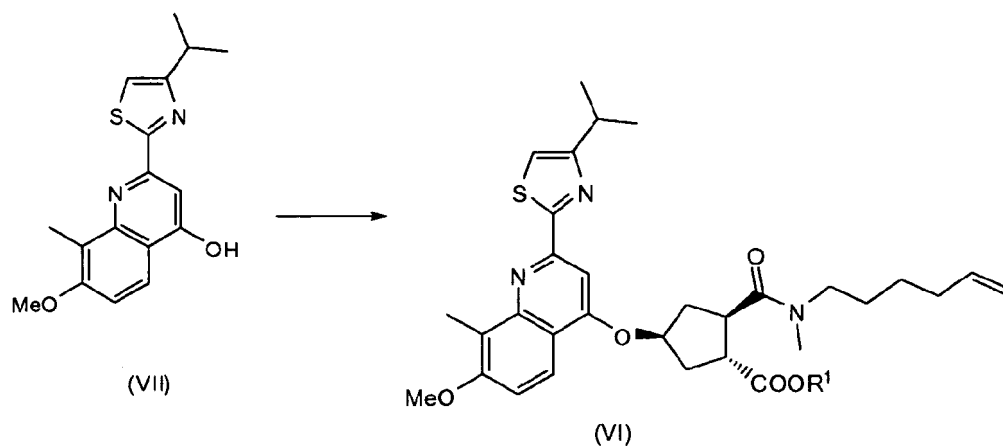


(I)

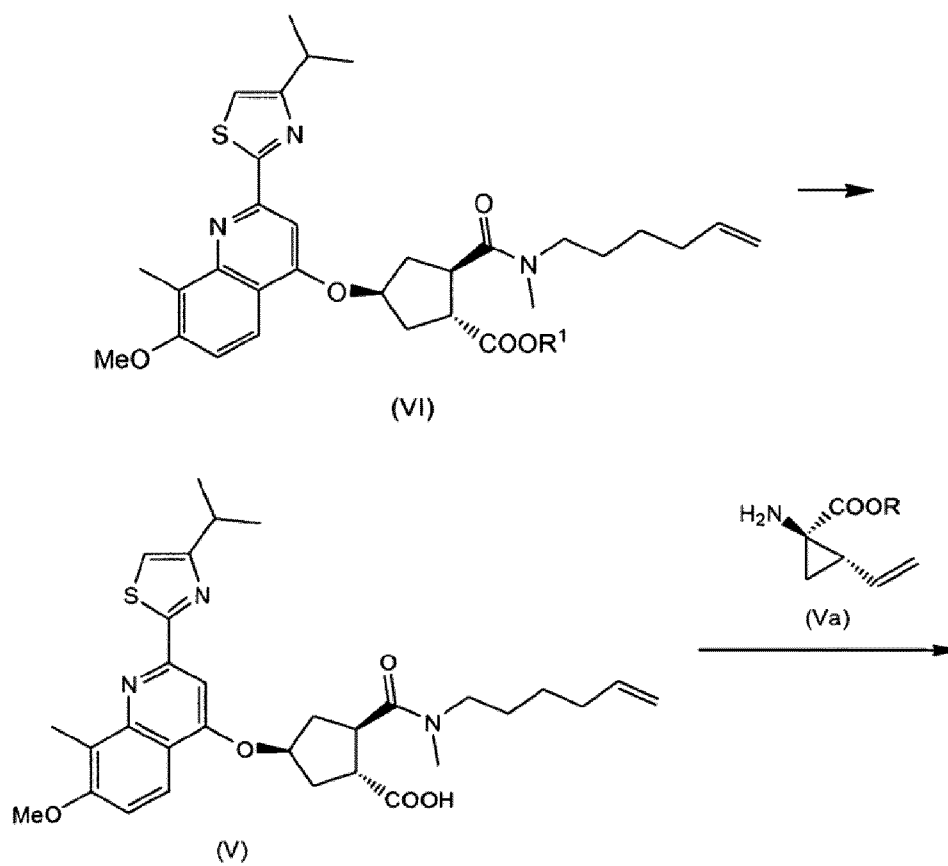
lequel procédé comprend un procédé de préparation d'un composé de formule (VIII) selon l'une quelconque des revendications 1 à 11, suivi d'une transformation en un composé de formule (I).

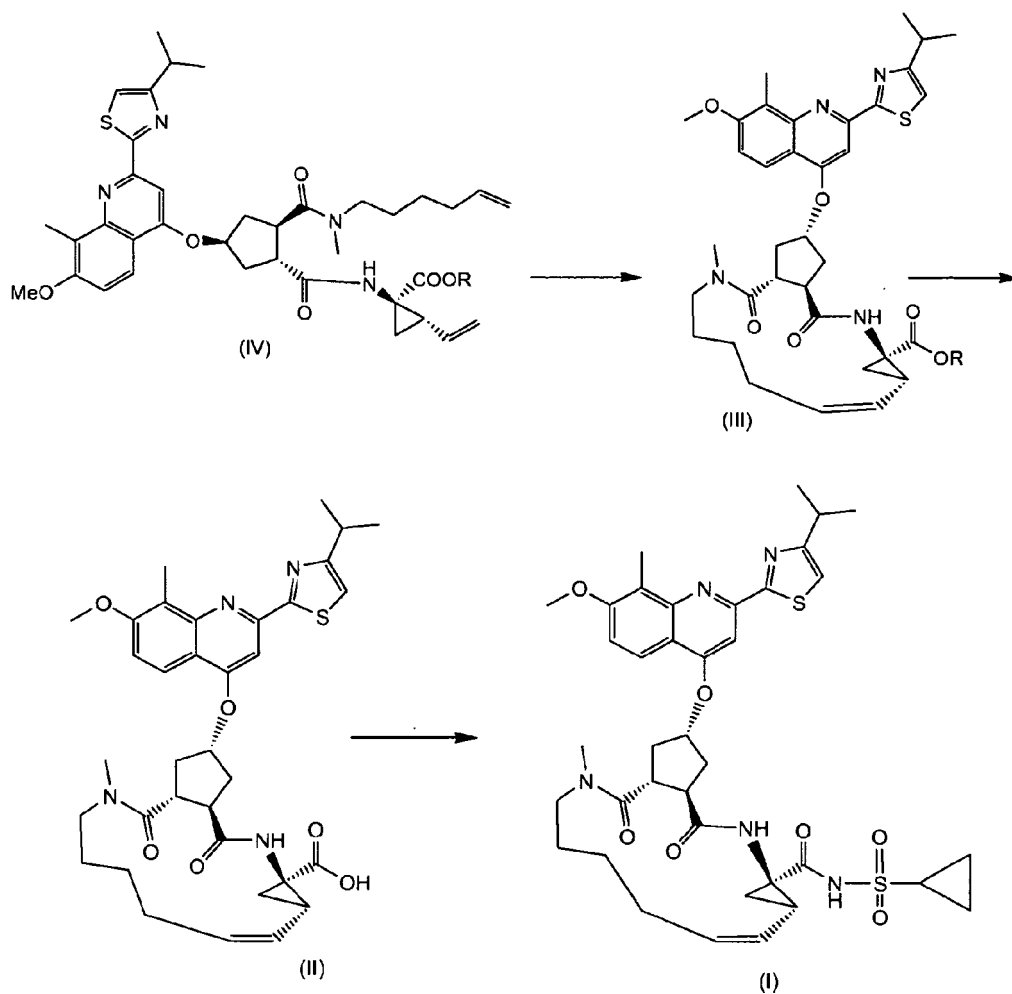
25. Procédé selon la revendication 24, **caractérisé en ce que** la transformation en composé de formule (I) est comme suit :

(i) la réaction d'un composé de formule (VIII) avec un composé de formule (VII) pour former un composé de formule (VI),



(ii) la transformation de (VI) en (I) conformément au schéma suivant :





26. Procédé de préparation d'un composé de formule (I), tel que défini dans la revendication 24, lequel procédé comprend un procédé de préparation d'un composé de formule (XXa) selon l'une quelconque des revendications 12 à 21, suivi d'une transformation en un composé de formule (1).
27. Procédé selon la revendication 26, **caractérisé en ce que** le composé de formule (XXa) est d'abord transformé en un composé de formule (VIII) en suivant un procédé selon l'une quelconque des revendications 1 à 11.
28. Procédé selon la revendication 27, **caractérisé en ce que** la transformation du composé de formule (VIII) en composé de formule (I) est selon la revendication 25.
29. Utilisation du sel de cinchonidine (XXa) défini dans la revendication 22, en tant qu'intermédiaire dans la préparation du composé (I) tel que défini dans la revendication 24.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 05073195 A [0003]
- WO 05073216 A [0003]
- WO 2007014926 A [0004]
- WO 2008092955 A [0004] [0006] [0009] [0030] [0034]
- WO 2005073195 A [0014] [0015]

Non-patent literature cited in the description

- **HONDA et al.** *Tetrahedron Letters*, 1981, vol. 22 (28), 2679-2682 [0012]
- **ROSENQUIST et al.** *Acta Chemica Scandinavica*, 1992, vol. 46, 1127-1129 [0014]